

United States Patent [19]

Clough et al.

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[54] **FUNGICIDES**

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[30] **Foreign Application Priority Data**

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[51] Int. Cl.⁴ C07D 241/44; C07D 241/18;
A01N 43/60

[52] U.S. Cl. 514/255; 514/249;
544/405; 544/408; 544/354

[58] Field of Search 544/405, 408, 354;
514/255, 249

[56] **References Cited**

U.S. PATENT DOCUMENTS

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0178826 4/1986 European Pat. Off. .

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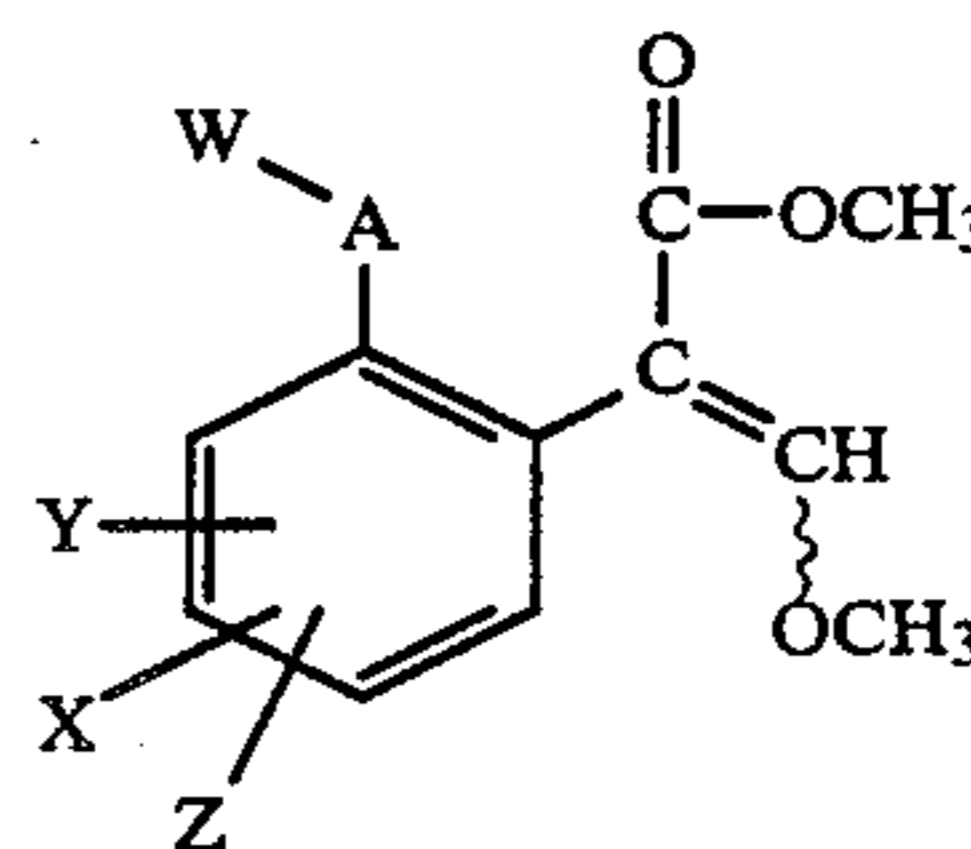
0242070 10/1987 European Pat. Off. .

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Attorney, Agent, or Firm—Cushman, Darby & Cushman

[57] **ABSTRACT**

This invention relates to derivatives of acrylic acid of the formula:



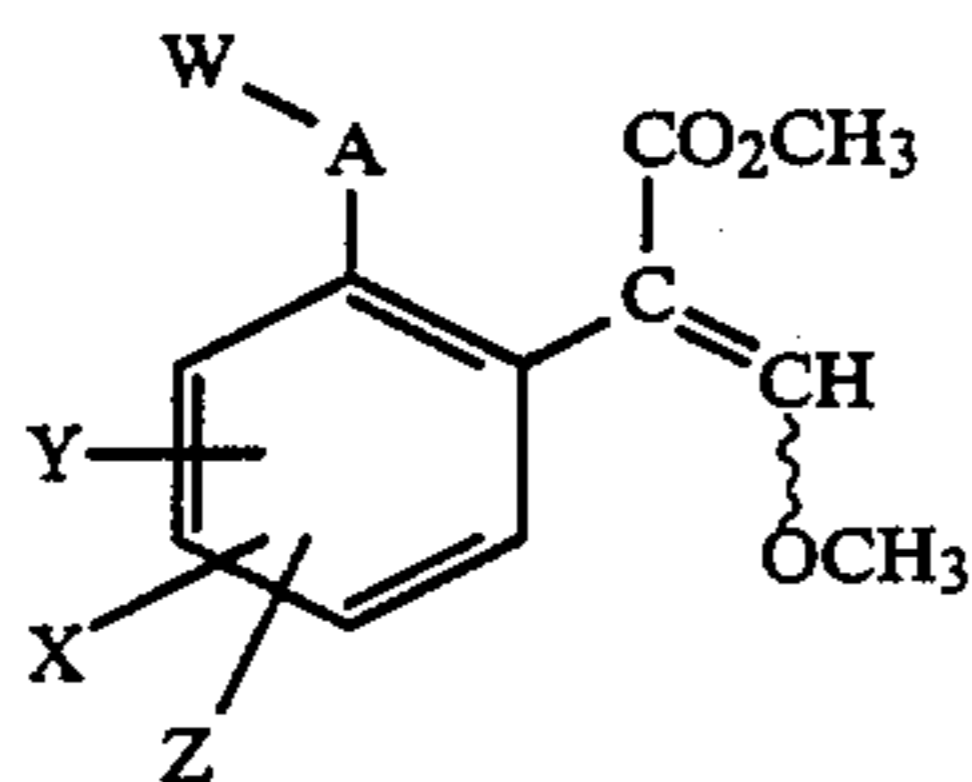
useful as fungicides, to processes for preparing them, to fungicidal compositions containing them, and to methods of using them to combat fungi, especially fungal infections in plants. The values of the variables are provided herein.

6 Claims, No Drawings

FUNGICIDES

This invention relates to derivatives of acrylic acid useful as fungicides, to processes for preparing them, to fungicidal compositions containing them, and to methods of using them to combat fungi, especially fungal infections in plants.

The invention provides a compound having the general formula (I):



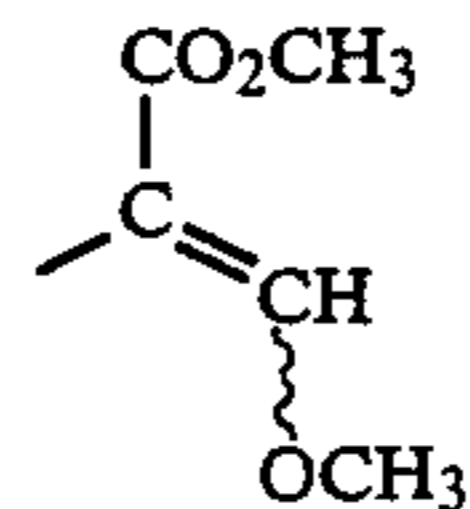
and stereoisomers thereof, wherein X, Y and Z, which are the same or different, are hydrogen, halogen, hydroxy, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted aralkyl, optionally substituted arylalkoxy, optionally substituted aryloxyalkyl, optionally substituted acyloxy, optionally substituted amino, acylamino, cyano, nitrile, $-\text{CO}_2\text{R}^1$, $-\text{CONR}^2\text{R}^3$, or $-\text{COR}^4$, or X and Y, when they are in adjacent positions on the phenyl ring, join to form a fused ring, either aromatic or aliphatic, optionally containing one or more heteroatoms; W is a C-linked optionally substituted six membered heterocyclic ring other than pyrimidinyl, containing two to four nitrogen atoms, and wherein adjacent substituents may together form a fused aromatic or hetero-aromatic ring; A is oxygen or sulphur; and R^1 , R^2 , R^3 , and R^4 , which are the same or different, are hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, optionally substituted aryl or optionally substituted aralkyl; and metal complexes thereof.

The compounds of the invention contain at least one carbon-carbon double bond, and are sometimes obtained in the form of mixtures of geometric isomers. However, these mixtures can be separated into individual isomers, and this invention embraces such isomers and mixtures thereof in all proportions including those which consist substantially of the (E)-isomer and those which consist substantially of the (Z)-isomer.

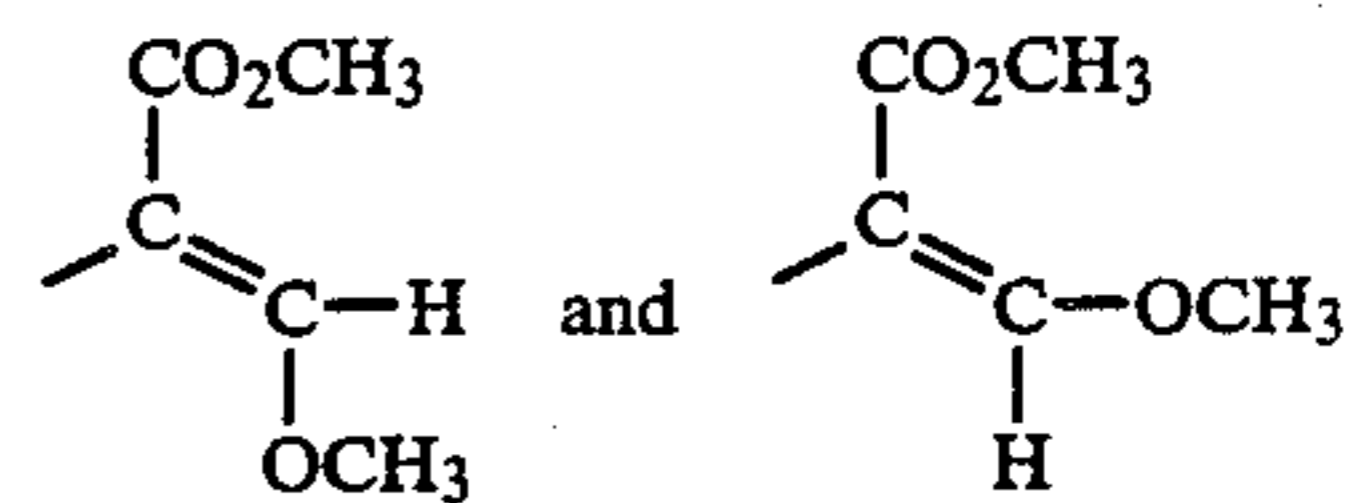
The individual stereoisomers which result from the unsymmetrically substituted double bond of the acrylate group are identified by the commonly used terms "(E)" and "(Z)". These terms are defined according to the Cahn-Ingold-Prelog system which is fully described in the literature (see, for example, J March, "Advanced Organic Chemistry," 3rd edition, Wiley-Interscience, page 109 et seq).

Usually one isomer is more fungicidally active than the other; the more active isomer being the one in which the group $-\text{OCH}_3$ is on the same side of the double bond as the substituted phenyl ring. In the case of the compounds of the present invention this is the (E)-isomer. These isomers form a preferred embodiment of the invention.

The formula:



used hereinafter signifies a separable mixture of both geometric isomers about the acrylate double bond, i.e.



Alkyl, wherever present as a group or moiety (in, for example, "alkoxy" and "aralkyl") can be in the form of straight or branched chains, and preferably contains 1 to 6, more preferably 1 to 4, carbon atoms; examples are methyl, ethyl, propyl, (n- or iso-propyl) and butyl (n-, sec-, iso- or t-butyl). Optional substituents of alkyl include hydroxy, halogen (especially chlorine and fluorine), C_{1-4} alkoxy and C_{1-4} alkoxycarbonyl.

Preferred substituent haloalkyl groups are halo- (C_{1-4}) alkyl groups and the same applies for preferred haloalkoxy groups. Of particular interest are trifluoromethyl and trifluoromethoxy. Cycloalkyl is preferably C_{3-6} cycloalkyl and includes cyclohexyl. Cycloalkylalkyl is preferably C_{3-6} cycloalkyl (C_{1-4}) alkyl, for example, cyclopropylethyl.

Aralkyl itself and the aralkyl moiety of arylalkoxy include, particularly, phenylalkyl (especially benzyl, phenylethyl, phenylpropyl, phenylbutyl or phenylhexyl) in which the alkyl moiety may carry other substituents such as hydroxy or C_{1-4} alkoxy and the aryl moiety may be substituted with, for example, one or more of halogen (especially chlorine or fluorine), hydroxy, C_{1-4} alkyl (especially methyl), C_{1-4} alkoxy (especially methoxy), trifluoromethyl, trifluoromethoxy, optionally substituted phenoxy, optionally substituted benzyloxy, nitro, amino, phenyl, carboxy or a carboxylic acid ester, cyano, alkylcarbonylamino and methylenedioxy. Substituents which may be present on the phenoxy and benzyloxy groups include any of those other substituents which may be present on the aryl moiety of aralkyl.

Aryloxyalkyl includes, in particular, phenoxyalkyl (especially phenoxyethyl and phenoxyethyl) in which the alkyl moiety may carry other substituents such as methoxy and the aryl moiety may be substituted in the same way as the aryl moiety in aralkyl above.

Alkenyl and alkynyl groups preferably contain 2 to 6 carbon atoms and, more preferably, 2 to 4 carbon atoms in the form of straight or branched chains. Ethenyl, propenyl and butenyl are examples of alkenyl groups. Optional substituents of alkenyl include aromatic and heteroaromatic groups (such as phenyl, furyl, thienyl and pyridyl) which may themselves carry substituents such as those described for the aryl moiety of aralkyl above. These include halogen (especially chlorine or fluorine). Further, the terminal carbon atom of the alkenyl groups may form part of a 5- or 6-membered cycloalkyl ring. Alkynyl includes ethynyl and is optionally substituted by, for example, phenyl which may itself be substituted as for the aryl moiety of aralkyl above.

Aryl itself and the aryl moiety of aryloxy are preferably phenyl. They may be substituted in the same way as the aryl moiety of aralkyl above.

Optional substituents which may be carried by an amino group include one or two of N-aryl and N-alkyl groups (such as N-phenyl or N-methyl).

Acyl itself and the acyl moiety of acyloxy include, in particular, acetyl and benzoyl in which the benzene ring may be substituted in the same way as the aryl moiety in aralkyl above. Acylamino includes benzoylamino, furoylamino and thienylcarbonylamino optionally substituted by, for example, N-alkyl (especially N-methyl).

Heterocyclic groups which W may include pyrazinyl, benzopyrazin-2-yl, pyridazin-3-yl, pyridazin-4-yl, cinnolin-3-yl, cinnolin-4-yl, 1,2,3-triazin-4-yl, 1,2,3-triazin-5-yl, 1,2,4-triazin-3-yl, 1,2,4-triazin-5-yl, 1,2,4-triazin-6-yl, 1,3,5-triazinyl, 1,2,4-benzotriazin-3-yl and 1,2,4,5-tetrazinyl.

The foregoing may bear one or more ring substituents or, in the case of a fused ring system may bear one or more substituents on either, or both, rings. Examples of

such substituents are halogen, nitro, C₁₋₄ alkyl optionally substituted with hydroxy or C₁₋₄ alkoxy, C₁₋₄alkoxy, optionally substituted with halogen, hydroxy or C₁₋₄ alkoxy, phenoxy, optionally substituted with halogen, hydroxy, amino, optionally substituted with C₁₋₄ alkyl, or cyano.

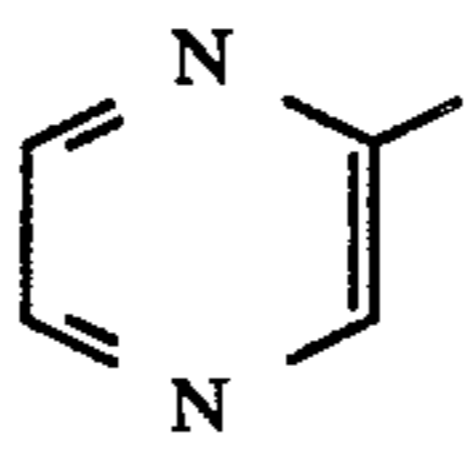
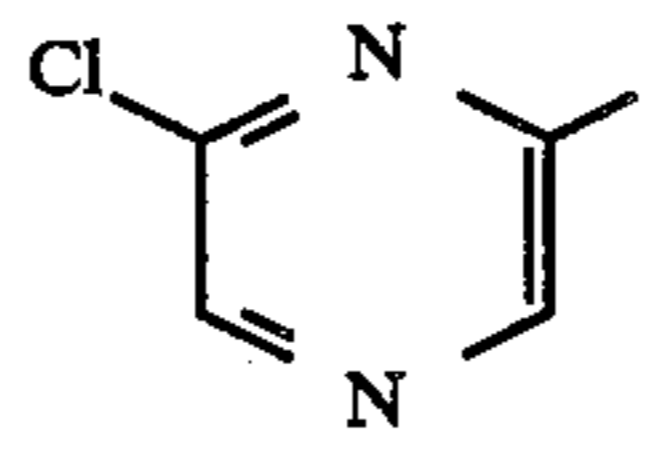
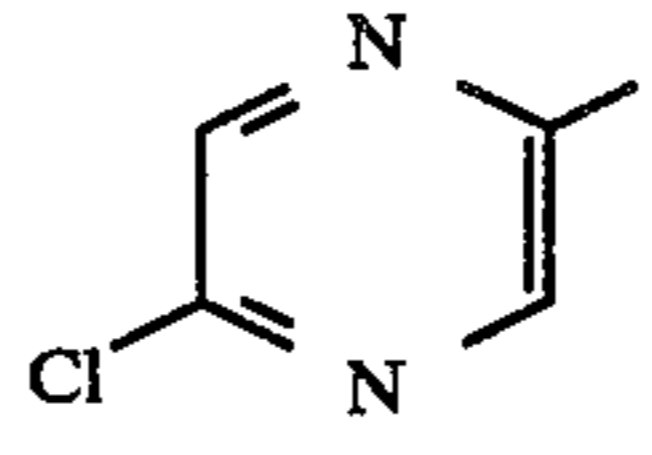
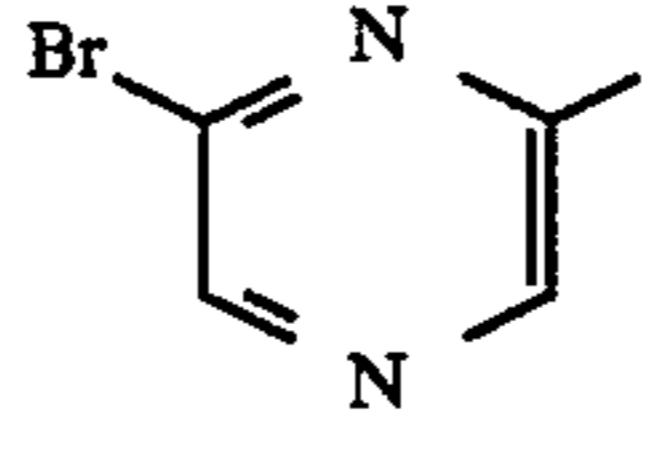
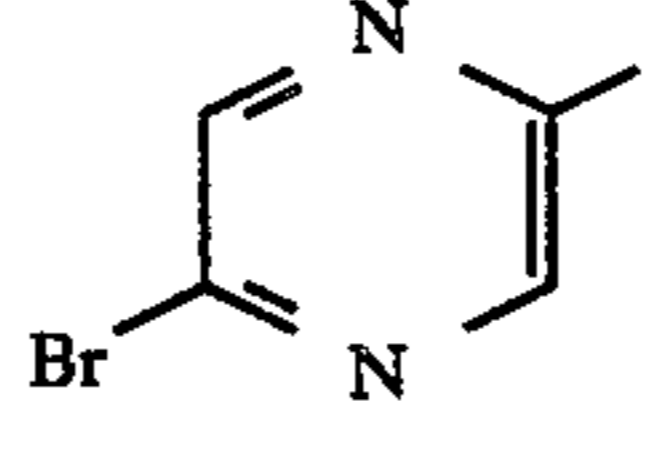
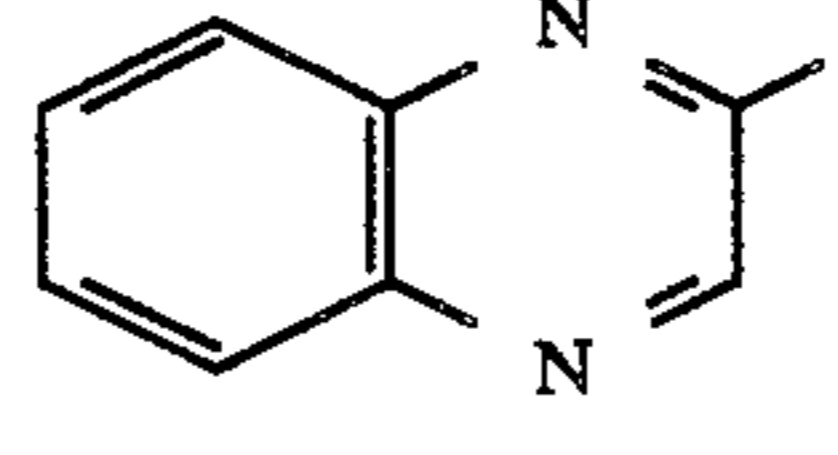
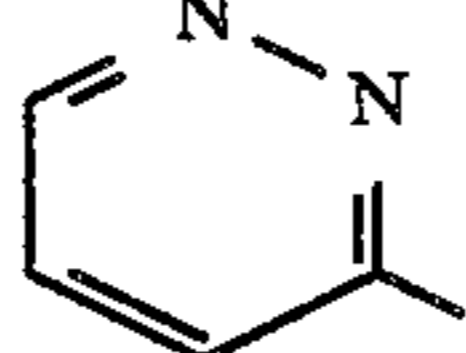
Values of W of particular interest are pyrazinyl and 1,3,5-triazinyl optionally substituted as indicated above. Typical substituents are chlorine, bromine, methyl, methoxy and nitro attached to any of the ring carbon atoms.

With all values of W it is preferred that X, Y and Z, which are the same or different, are single atoms or sterically small groups such as fluoro, chloro, bromo, hydroxy, methyl, methoxy, trifluoromethyl, methylamino or dimethylamino but are more preferably hydrogen.

A is preferably oxygen.

The invention is illustrated by the compounds presented in Table I below.

TABLE I

Compound No.	W	A	X	Y	Z	Melting Point (°C.)	Olefinic*	Isomer ⁺
1		O	H	H	H			<u>E</u>
2		O	H	H	H	Oil	7.50	<u>E</u>
3		O	H	H	H			<u>E</u>
4		O	H	H	H			<u>E</u>
5		O	H	H	H			<u>E</u>
6		O	H	H	H			<u>E</u>
7		O	H	H	H			<u>E</u>

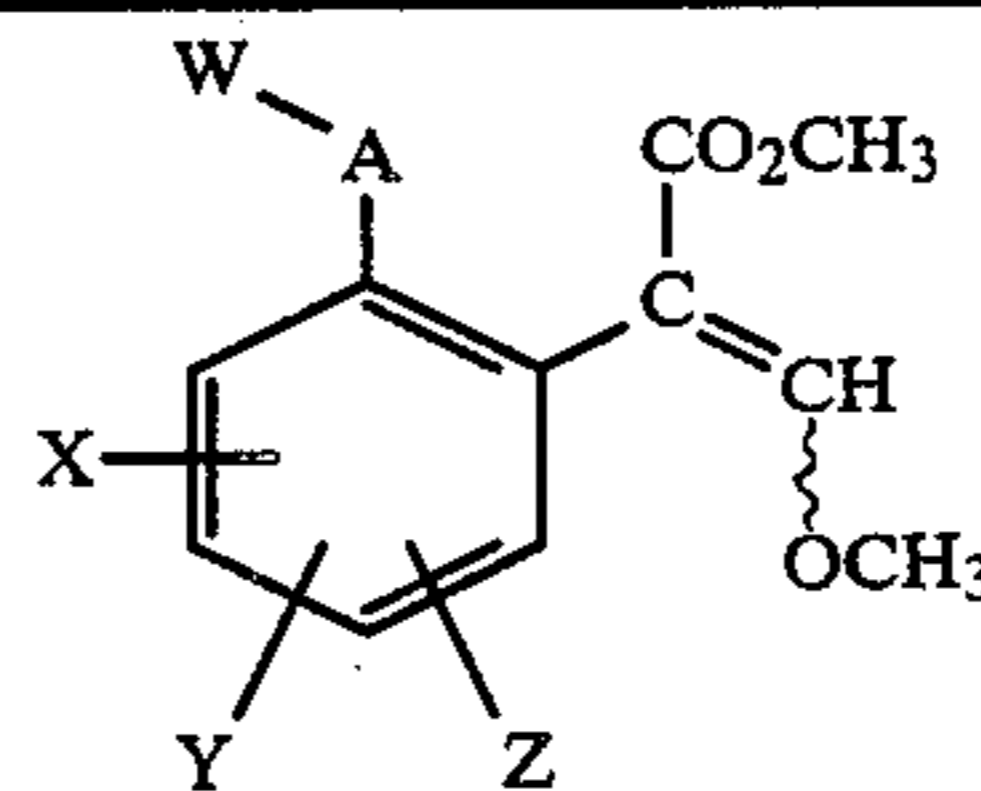
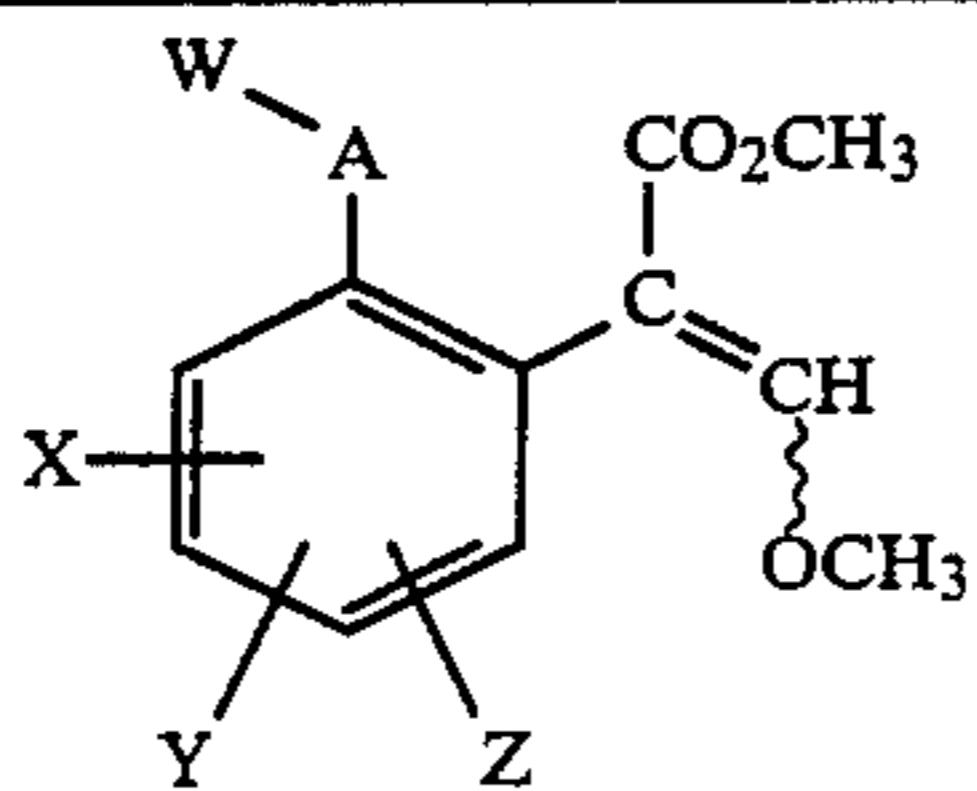
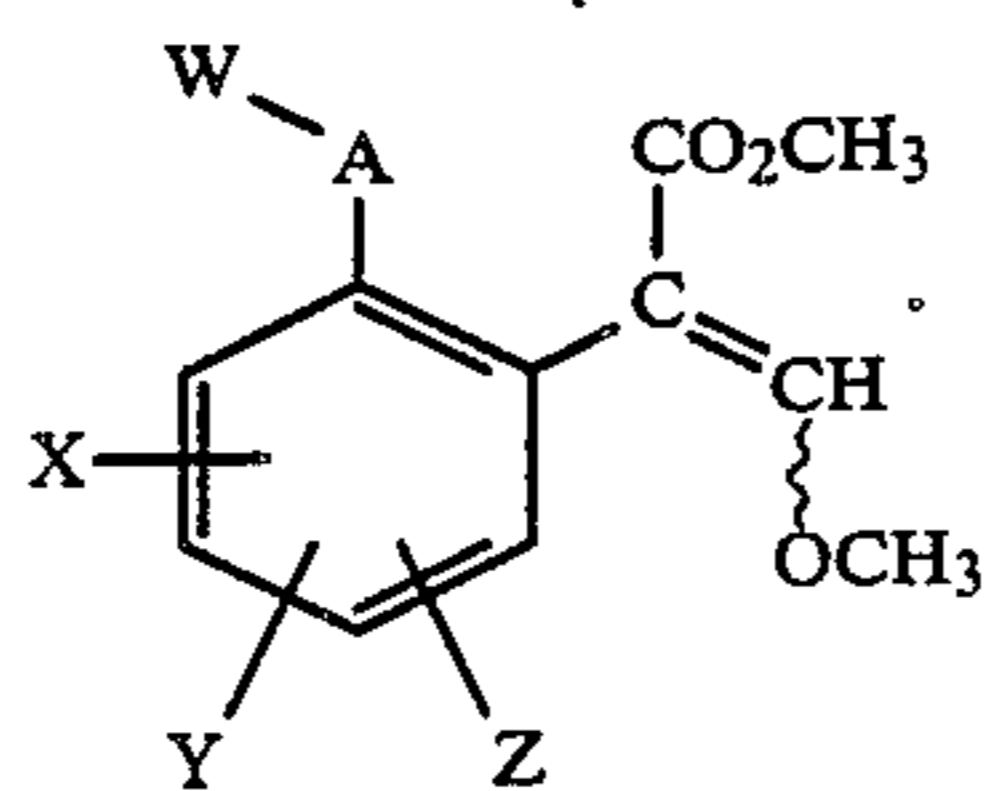


TABLE I-continued



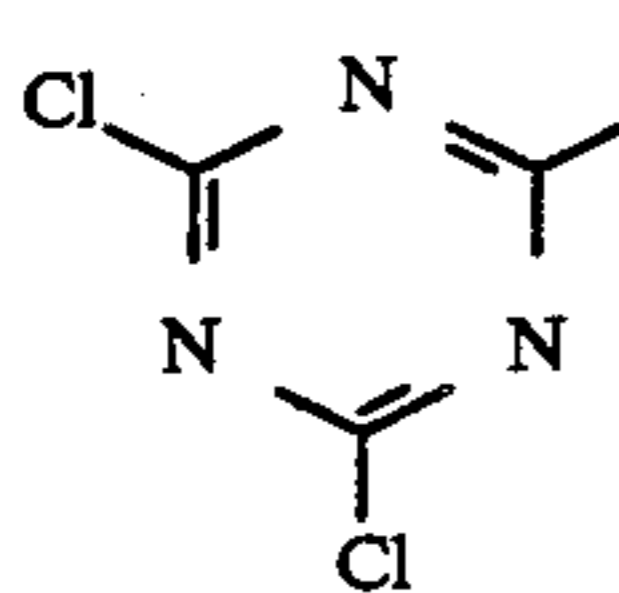
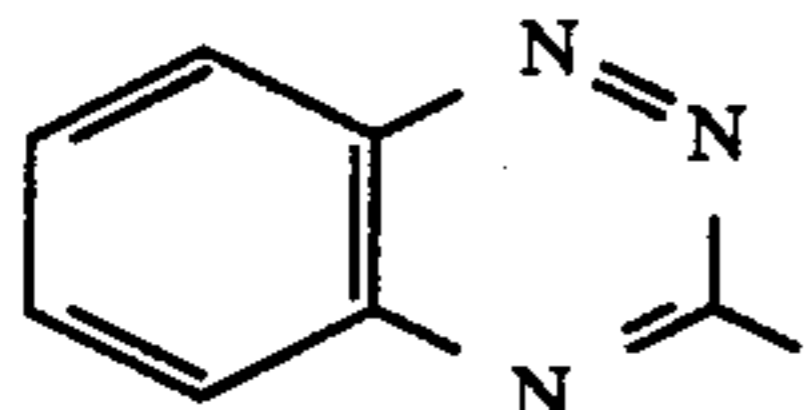
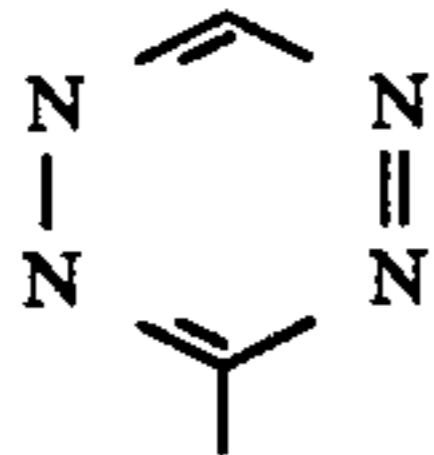
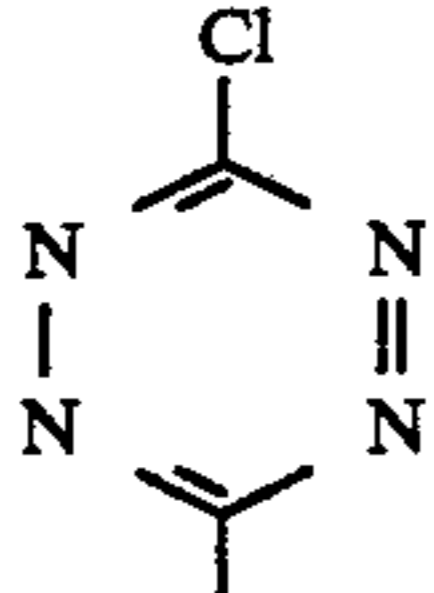
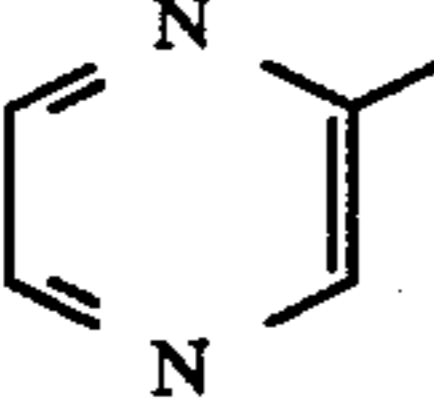
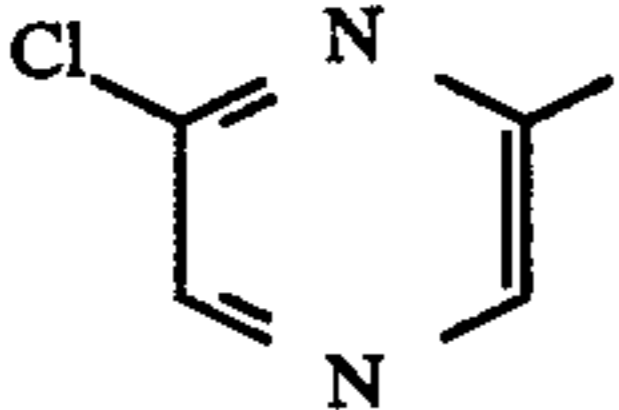
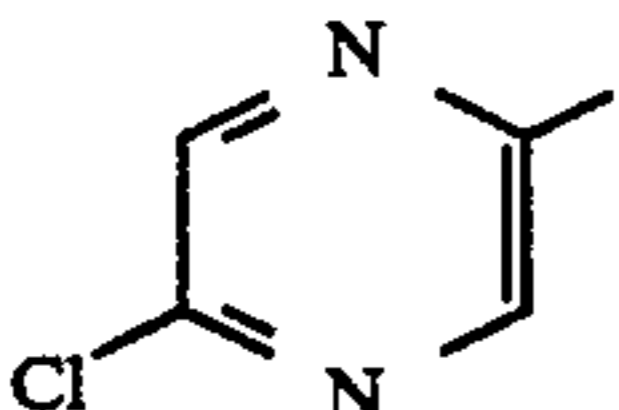
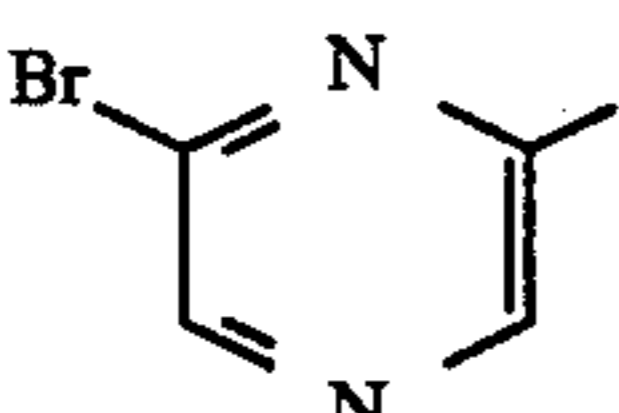
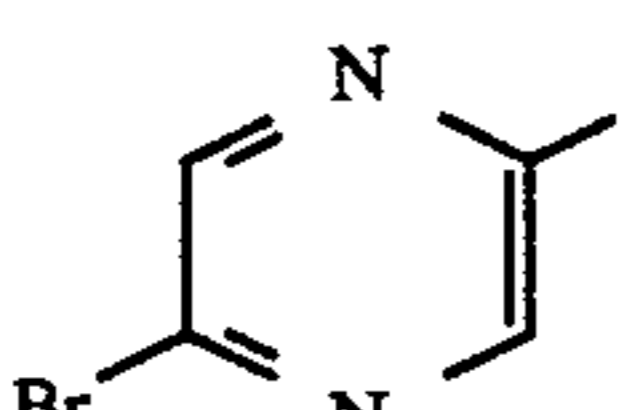
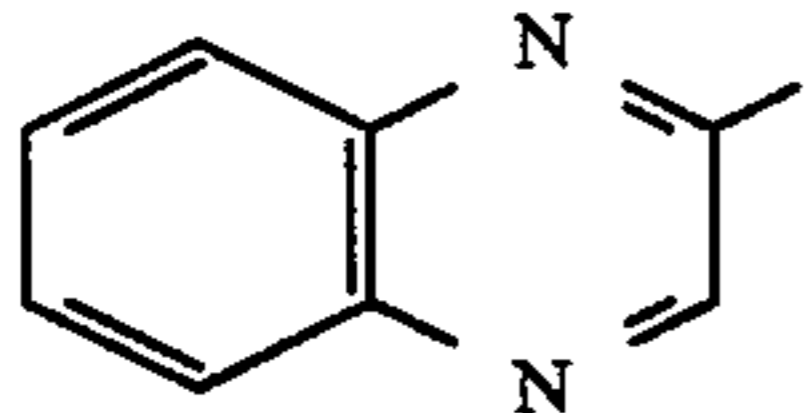
Compound No.	W	A	X	Y	Z	Melting Point (°C.)	Olefinic*	Isomer ⁺
8		O	H	H	H			<u>E</u>
9		O	H	H	H			<u>E</u>
10		O	H	H	H			<u>E</u>
11		O	H	H	H			<u>E</u>
12		O	H	H	H			<u>E</u>
13		O	H	H	H			<u>E</u>
14		O	H	H	H			<u>E</u>
15		O	H	H	H			<u>E</u>
16		O	H	H	H			<u>E</u>
17		O	H	H	H			<u>E</u>
18		O	H	H	H			<u>E</u>

TABLE I-continued



Compound No.	W	A	X	Y	Z	Melting Point (°C.)	Olefinic*	Isomer ⁺
19		O	H	H	H			<u>E</u>
20		O	H	H	H			<u>E</u>
21		O	H	H	H			<u>E</u>
22		O	H	H	H			<u>E</u>
23		O	H	H	H			<u>E</u>
24		O	H	H	H			<u>E</u>
25		O	H	H	H			<u>E</u>
26		O	H	H	H			<u>E</u>
27		O	H	H	H			<u>E</u>
28		O	H	H	H			<u>E</u>

TABLE I-continued

Compound No.	W	A	X	Y	Z	Melting Point (°C.)	Olefinic*	Isomer ⁺
29		O	H	H	H	141-142.5	7.46	<u>E</u>
30		O	H	H	H			<u>E</u>
31		O	H	H	H			<u>E</u>
32		O	H	H	H			<u>E</u>
33		S	H	H	H			<u>E</u>
34		S	H	H	H			<u>E</u>
35		S	H	H	H			<u>E</u>
36		S	H	H	H			<u>E</u>
37		S	H	H	H			<u>E</u>
38		S	H	H	H			<u>E</u>

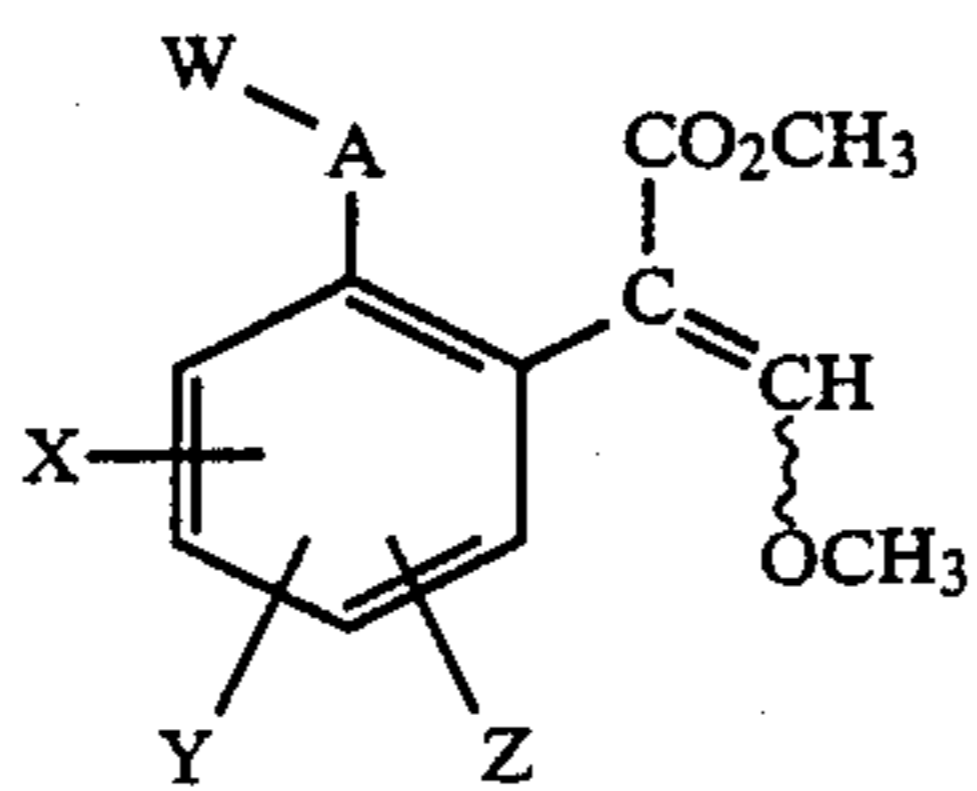
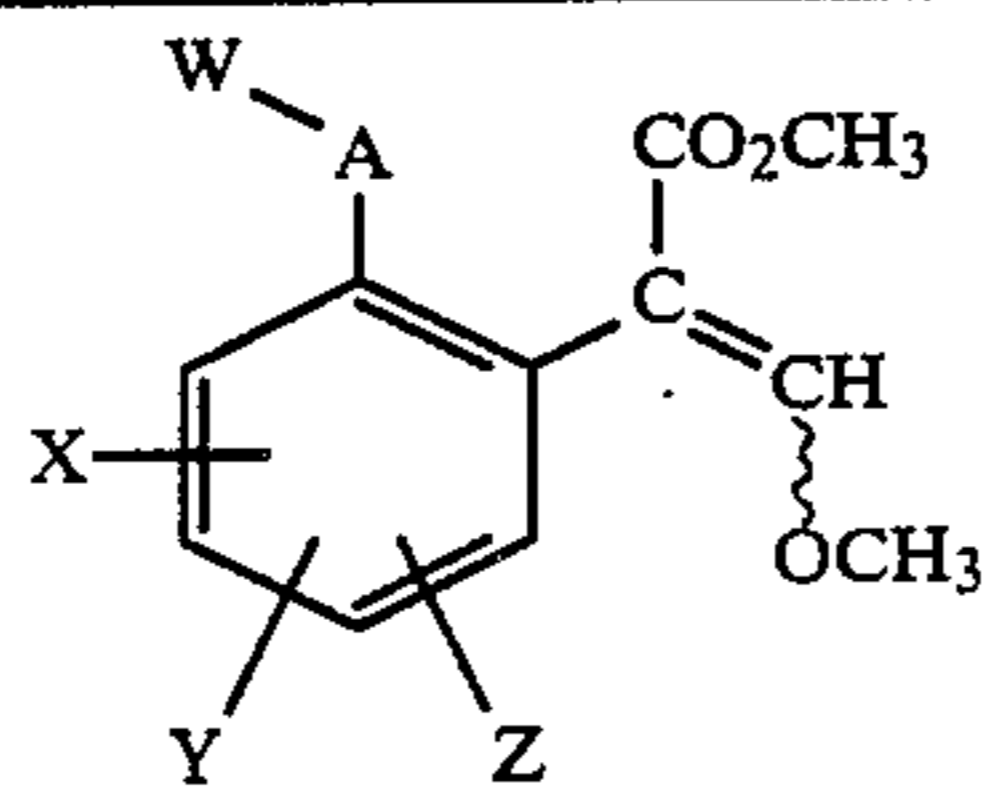
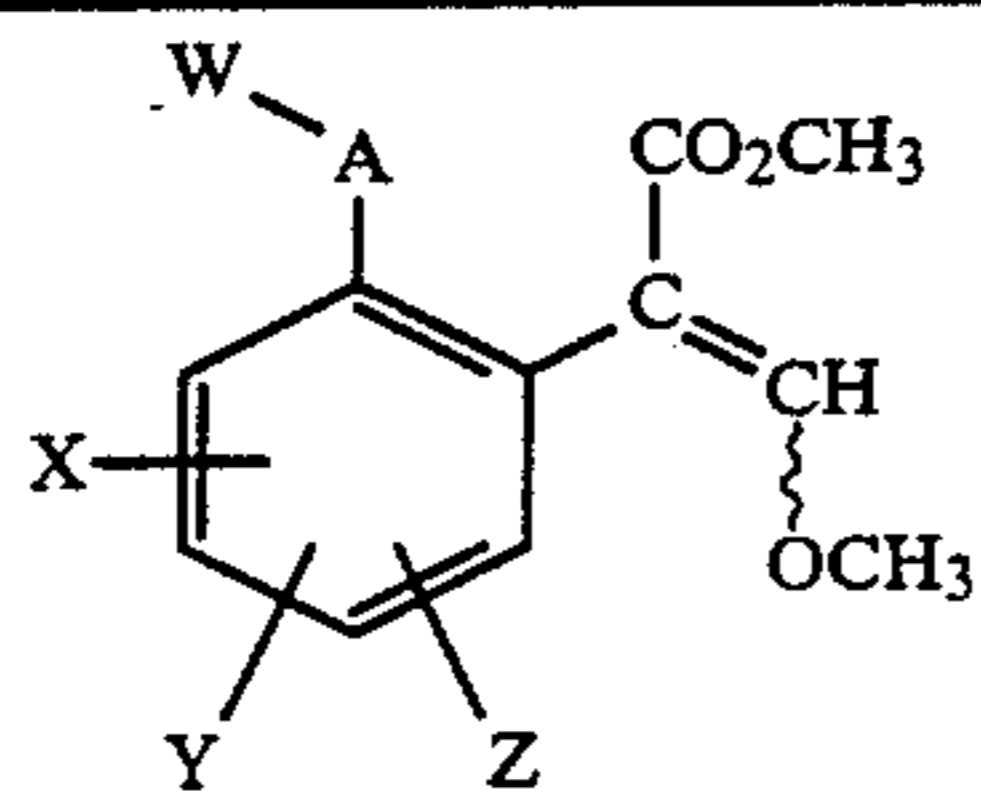


TABLE I-continued



Compound No.	W	A	X	Y	Z	Melting Point (°C.)	Olefinic*	Isomer ⁺
39		S	H	H	H			<u>E</u>
40		S	H	H	H			<u>E</u>
41		S	H	H	H			<u>E</u>
42		S	H	H	H			<u>E</u>
43		S	H	H	H			<u>E</u>
44		S	H	H	H			<u>E</u>
45		S	H	H	H			<u>E</u>
46		S	H	H	H			<u>E</u>
47		S	H	H	H			<u>E</u>
48		S	H	H	H			<u>E</u>
49		S	H	H	H			<u>E</u>

TABLE I-continued



Compound No.	W	A	X	Y	Z	Melting Point (°C.)	Olefinic*	Isomer ⁺
50		S	H	H	H			<u>E</u>
51		S	H	H	H			<u>E</u>
52		S	H	H	H			<u>E</u>
53		S	H	H	H			<u>E</u>
54		S	H	H	H			<u>E</u>
55		S	H	H	H			<u>E</u>
56		S	H	H	H			<u>E</u>
57		S	H	H	H			<u>E</u>
58		S	H	H	H			<u>E</u>
59		S	H	H	H			<u>E</u>
60		S	H	H	H			<u>E</u>

TABLE I-continued

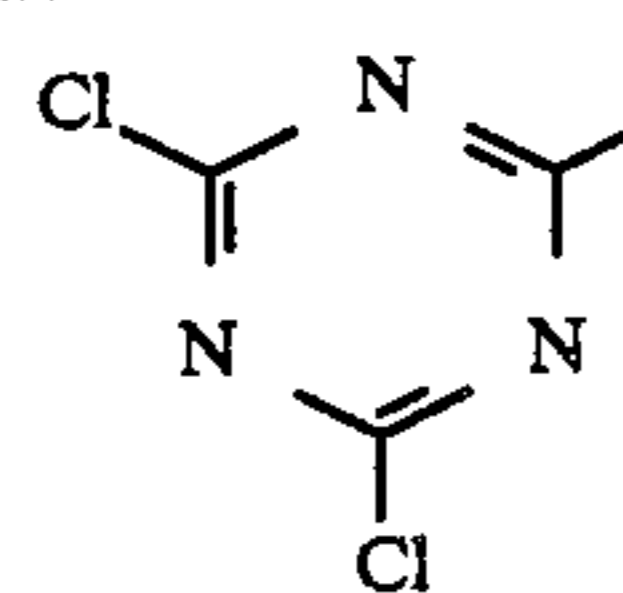
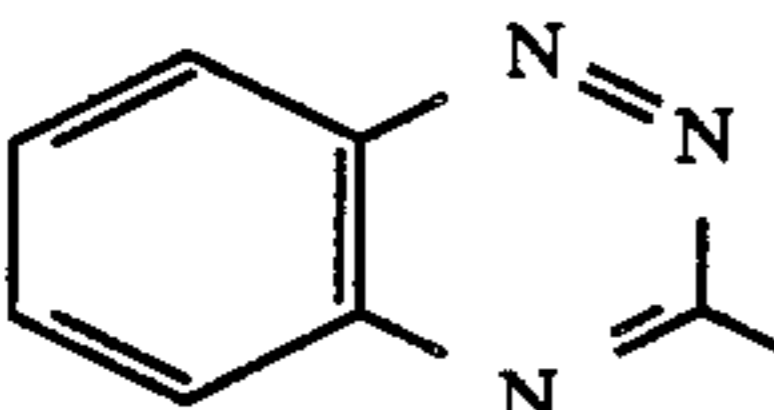
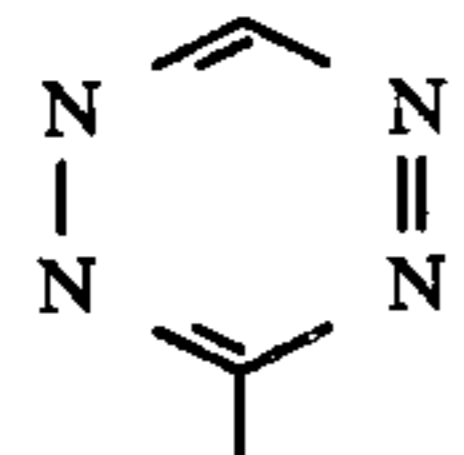
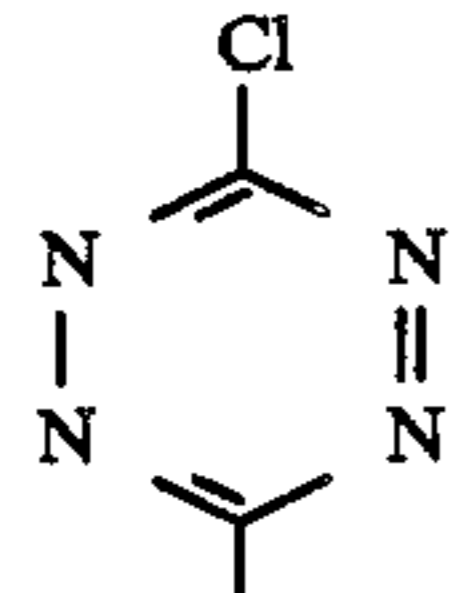
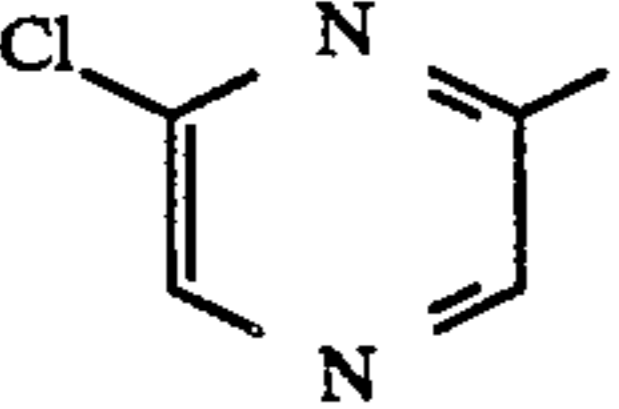
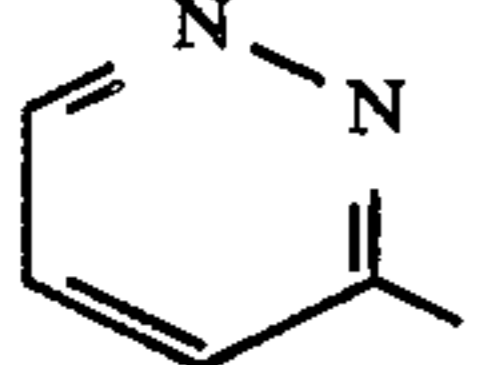
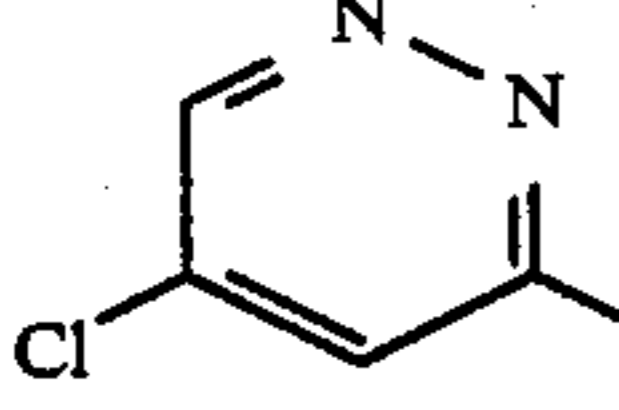
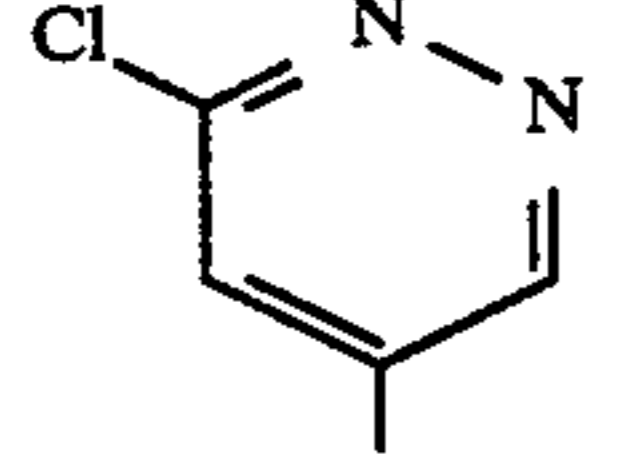
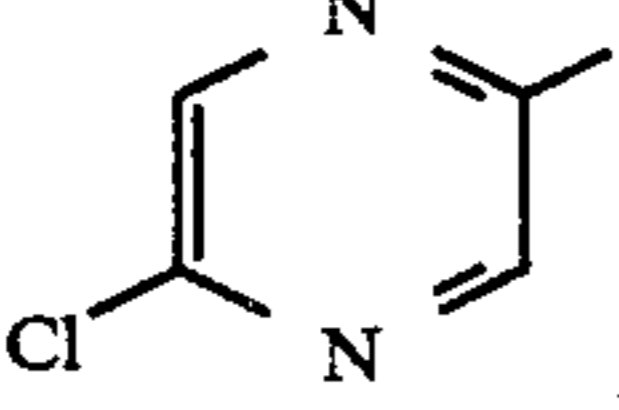
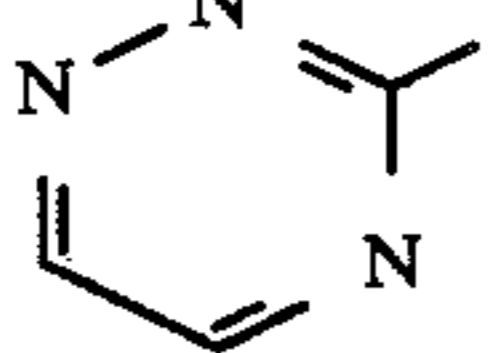
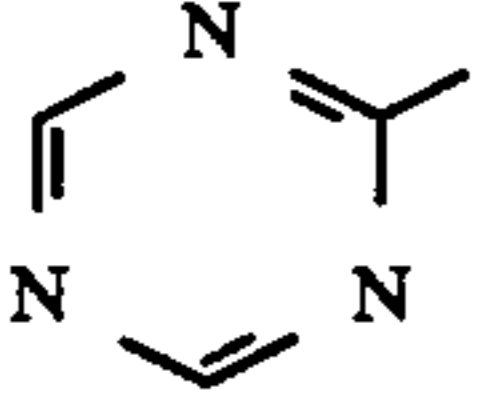
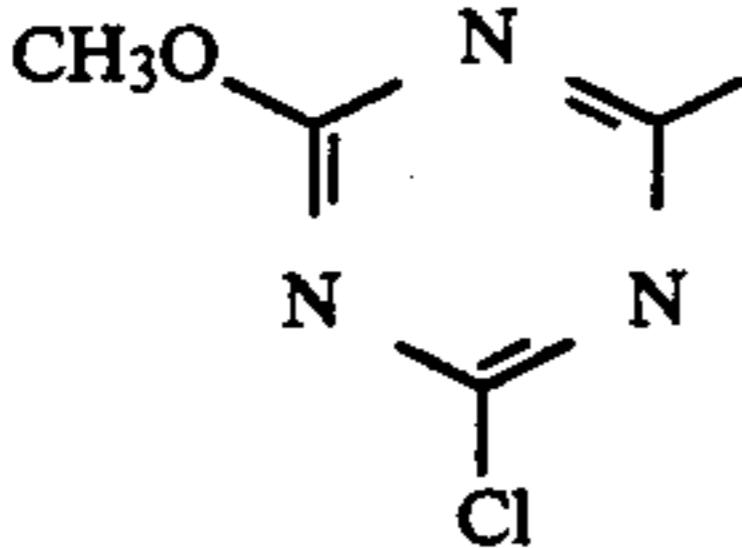
Compound No.	W	A	X	Y	Z	Melting Point (°C.)	Olefinic*	Isomer ⁺
61		S	H	H	H			<u>E</u>
62		S	H	H	H			<u>E</u>
63		S	H	H	H			<u>E</u>
64		S	H	H	H			<u>E</u>
65		O	3-Cl	H	H			<u>E</u>
66		O	5-Cl	H	H			<u>E</u>
67		O	4-F	H	H			<u>E</u>
68		O	6-F	H	H			<u>E</u>
69		S	4-CH ₃	H	H			<u>E</u>
70		S	4-CH ₃ O	H	H			<u>E</u>

TABLE I-continued

Compound No.	W	A	X	Y	Z	Melting Point (°C.)	Olefinic*	Isomer [†]
71		S	4-NO ₂	H	H			<u>E</u>
72		O	H	H	H	121-123	7.45	<u>E</u>

*Chemical shift of singlet from olefinic proton on beta-methoxyacrylate group (ppm from tetramethylsilane). Solvent CDCl₃.

[†]Geometry of beta-methoxyacrylate.

The compounds of the invention having the general formula (I) can be prepared from substituted phenols or thiophenols of general formula (VII) by the steps shown in Scheme I. Throughout Scheme I the terms A, X, Y, Z and W are as defined above, and L is a halogen atom or another good leaving group.

Thus, compounds of general formula (I), which exist as geometric isomers which may be separated by chromatography, fractional crystallisation or distillation, can be prepared by O-methylation of compounds of general formula (III) using a base (such as potassium carbonate) and a methylating agent CH₃-L (II) in a suitable solvent (such as N,N-dimethylformamide) (Step (a) of Scheme I).

Compounds of general formula (III) can be prepared by treating phenylacetates of general formula (IV) with a base (such as sodium hydride) and a formic ester (such as methyl formate) in a suitable solvent (such as N,N-dimethyl formamide) (Step (b) of Scheme I).

Alternatively, compounds of general formula (I) can be prepared from acetals of general formula (XIII) by elimination of methanol under either acidic or basic conditions, at a suitable temperature and often in a suitable solvent (step (c) of Scheme I). Examples of reagents or reagent mixtures which can be used for this transformation are lithium di-isopropylamide; potassium hydrogen sulphate (see, for example, T Yamada, H Hagiwara and H Uda, *J. Chem. Soc., Chemical Communications*, 1980, 838, and reference therein); and triethylamine, often in the presence of a Lewis acid such as titanium tetrachloride (see, for example, K Nsunda and L. Heresi, *J. Chem. Soc., Chemical Communications*, 1985, 1000).

Acetals of general formula (XIII) can be prepared by treatment of methyl silyl ketene acetals of general formula (XIV) wherein R is an alkyl group with trimethyl orthoformate in the presence of Lewis acid such as titanium tetrachloride, at a suitable temperature and in a suitable solvent (see, for example, K Saigo, M Osaki and T Mukaiyama, *Chemistry Letters*, 1976, 769).

Methyl silyl ketene acetals of general formula (XIV) can be prepared from esters of general formula (IV) by

treatment with a base and a trialkylsilyl halide of general formula R₃SiCl or R₃SiBr, such as trimethylsilyl chloride, or a base and a trialkylsilyl triflate of general formula R₃Si-OSO₂CF₃, in a suitable solvent and at a suitable temperature (see, for example, C Ainsworth, F Chen and Y Kuo, *J. Organometallic Chemistry*, 1972, 46, 59).

It is not always necessary to isolate the intermediates (XIII) and (XIV); under appropriate conditions, compounds of general formula (I) may be prepared from esters of general formula (IV) in "one pot" by the successive addition of suitable reagents listed above.

Compounds of general formula (IV) can be prepared by esterification of compounds of general formula (V) by standard methods described in the chemical literature (Step (d) of Scheme I).

Compounds of general formula (V) can be prepared by the reaction of compounds of general formula (VII) with compounds of formula (VI) in the presence of a base (such as potassium carbonate) and, if necessary, a transition metal or transition metal salt catalyst (such as copperbronze) in a convenient solvent (such as N,N-dimethylformamide) (Step (e) of Scheme I).

Alternatively, compounds of general formula (IV) can be prepared from esters of general formula (VIII) by reaction with compounds of general formula (VI) in the presence of a base (such as potassium carbonate) and, if necessary, a transition metal or transition metal salt catalyst (such as copper-bronze) in a convenient solvent (such as N,N-dimethylformamide) (Step (f) of Scheme I).

Esters of general formula (VIII) can be prepared by esterification of compounds of general formula (VII) by standard methods described in the chemical literature (Step (g) of Scheme I).

Compounds of general formula (VII) can be prepared by standard methods described in the chemical literature. (For example, see, A. Clesse, W. Haefliger, D. Hauser, H. U. Gubler, B. Dewald and M. Baggiolini, *J. Med. Chem.*, 1981, 24, 1465).

Alternatively, compounds of the invention having the general formula (I) can be prepared from phenylacetates of general formula (XII) by the steps shown in Scheme II. Throughout Scheme II the terms A, W, X, Y, Z and L are as defined above, and m is a protecting group for a phenol or thiophenol group.

Thus compounds of general formula (I) can be prepared by reaction of compounds of general formula (IX) with compounds of general formula (VI) in the presence of a base (such as potassium carbonate) and, if necessary, a transition metal or transition metal salt catalyst in a convenient solvent (such as N,N-dimethylformamide) (step (h) of Scheme II).

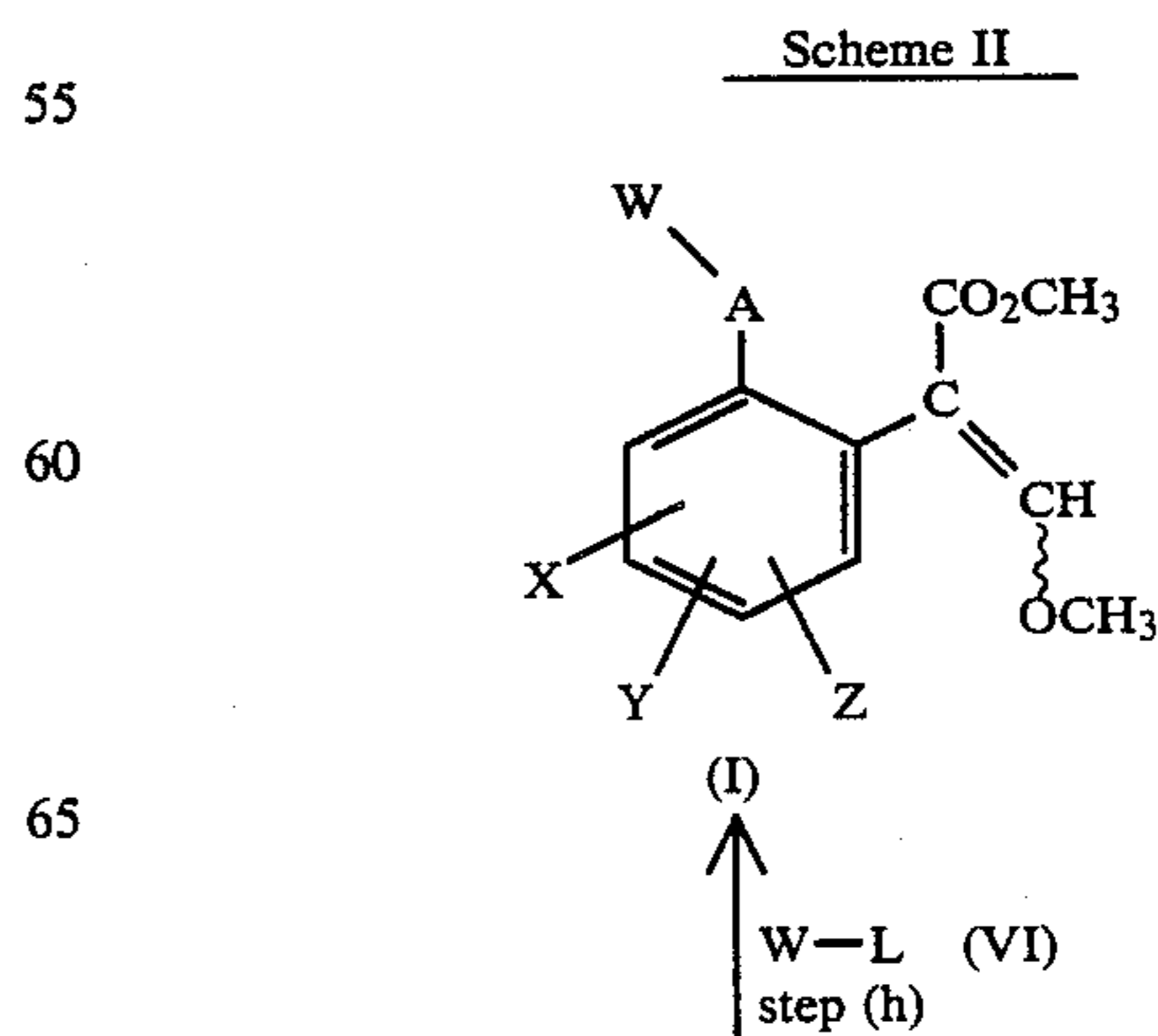
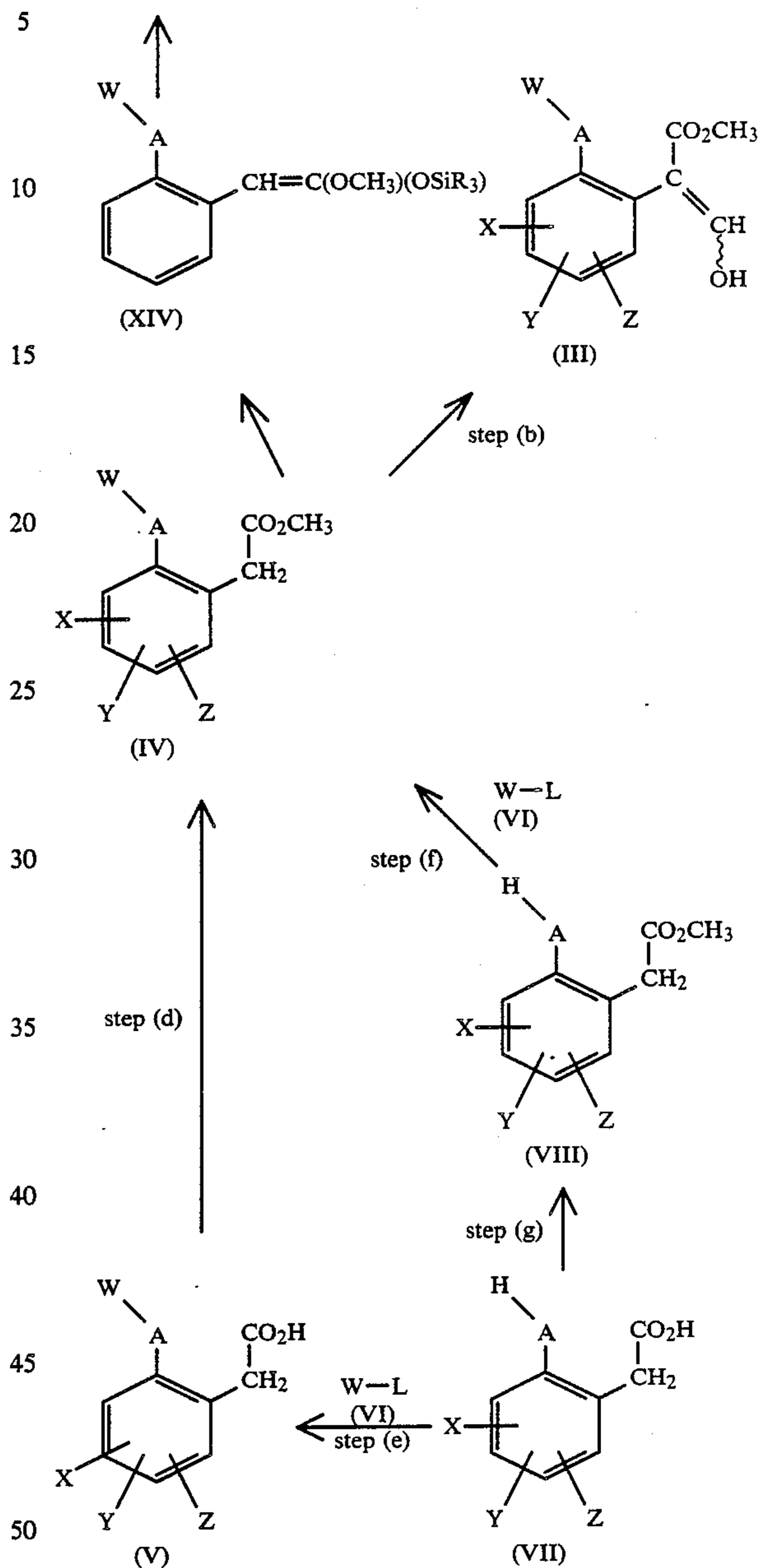
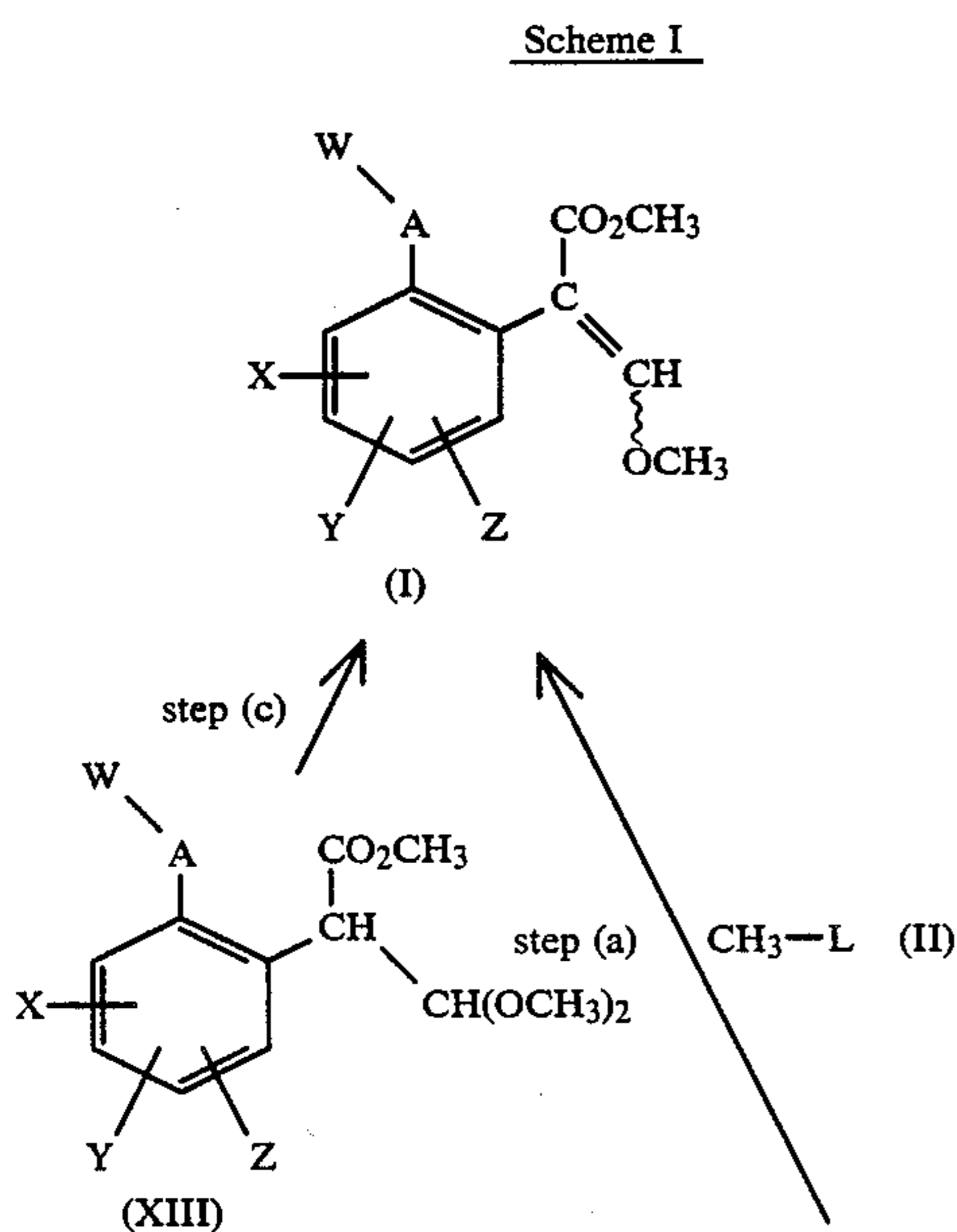
Compounds of general formula (IX) can be prepared from protected phenol or thiophenol derivatives of general formula (X) by standard deprotection procedures as set out in the chemical literature (step (i) of Scheme II). For example, phenols of general formula (IX, A=O) can be prepared from benzyl ethers of general formula (X, A=O, M=CH₂Ph) by hydrogenolysis in the presence of a suitable catalyst (such as palladium supported on carbon).

Compounds of general formula (X), in which the group M is a standard phenol or thiophenol protecting group (such as benzyl), can be prepared by O-methylation of compounds of general formula (XI) using a base (such as potassium carbonate) and a methylating agent CH₃-L (II) in a suitable solvent (such as N,N-dimethylformamide) (step (j) of Scheme II).

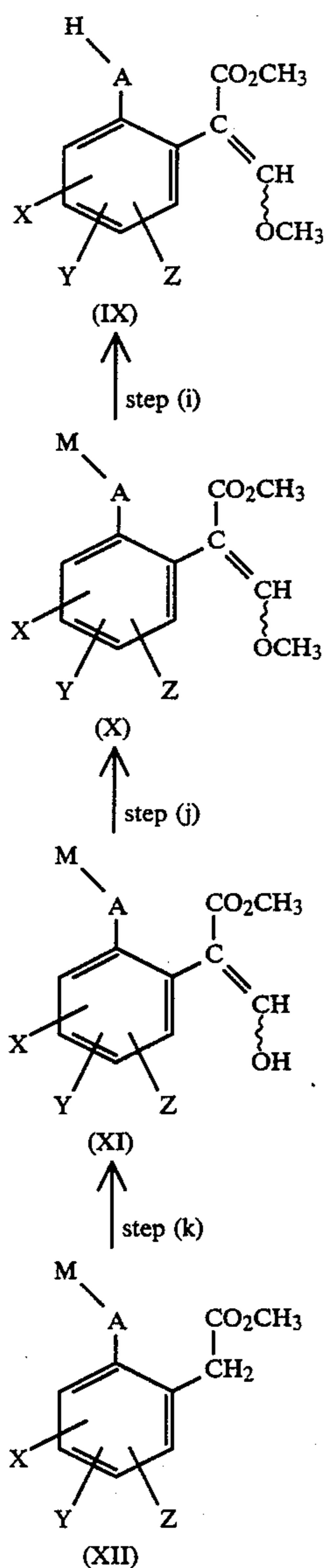
Compounds of general formula (XI) can be prepared by treating phenylacetates of general formula (XII) with a base (such as sodium hydride) and a formic ester (such as methyl formate) in a suitable solvent (such as N,N-dimethylformamide) (step (k) of Scheme II).

Compounds of general formula (XII) can be prepared from compounds of general formula (VIII) by standard methods described in the chemical literature.

In further aspects the invention provides processes as herein described for preparing compounds of formula (I). It also provides the intermediate chemicals of formulae (III)-(V), (XIII) and (XIV).



-continued
Scheme II



The compounds are active fungicides, and may be used to control one or more of the following pathogens:

Pyricularia oryzae on rice.

Puccinia recondita, *Puccinia striiformis* and other rusts on wheat, *Puccinia hordei*, *Puccinia striiformis* and other rusts on barley, and rusts on other hosts e.g. coffee, pears, apples, peanuts, vegetables and ornamental plants.

Erysiphe graminis (powdery mildew) on barley and wheat and other powdery mildews on various hosts such as *Sphaerotheca macularis* on hops, *Sphaerotheca fuliginea* on cucurbits (e.g. cucumber), *Podosphaera leucotricha* on apples and *Uncinula necator* on vines.

Helminthosporium spp., *Rhynchosporium* spp., *Septoria* spp. and *Pseudocercospora herpotrichoides*.

Cercospora arachidicola and *Cercosporidium personata* on peanuts and other *Cercospora* species on other hosts for example sugar beet, bananas, soya beans and rice.

Alternari species on vegetables (e.g. cucumber) oil, seed rape, apples, tomatoes and other hosts.

Venturia inaequalis (scab) on apples.

Plasmopara viticola on vines.

Other downy mildews such as *bremia lactucae* on lettuce, *Peronospora* spp. on soybeans, tobacco, onions and other hosts and *Pseudoperonospora humuli* on hops and *Pseudoperonospora cubensis* on cucurbits. *Phytophthora infestans* on potatoes and tomatoes and other *Phytophthora* spp. on vegetables, strawberries, avocado, pepper, ornamentals, tobacco, cocoa and other hosts.

Some of the compounds have also shown a broad range of activities against fungi in vitro. They may have activity against various post-harvest pathogens of fruit (e.g. *Penicillium digitatum* and *italicum* and *Trichoderma viride* on oranges, *Gloeosporium musarum* on bananas and *Botrytis cinerea* on grapes).

Further some of the compounds may be active as seed dressings against *Fusarium* spp., *Septoria* spp., *Tilletia* spp., (bunt, a seed borne disease of wheat), *Ustilago* spp., *Helminthosporium* spp. on cereals, *Rhizoctonia solani* on cotton and *Pyricularia oryzae* on rice.

The compounds can move acropetally in the plant tissue. Moreover, the compounds may be volatile enough to be active in the vapour phase against fungi on the plant.

The invention therefore provides a method of combating fungi, which comprises applying to a plant, to seed of a plant, or to the locus of the plant or seed, an effective amount of a compound of general formula (I) as hereinbefore defined, or a composition containing the same.

The compounds may also be useful as industrial (as opposed to agricultural) fungicides, e.g. in the prevention of fungal attack on wood, hides, leather and especially paint films.

The compounds may be used directly but are more conveniently formulated into compositions using a carrier or diluent. The invention thus provides a fungicidal composition comprising a compound of general formula (I) as hereinbefore defined, and a fungicidally acceptable carrier or diluent therefor.

The compounds, can be applied in a number of ways. For example they can be applied, formulated or unformulated, directly to the foliage of a plant, to seeds or to other medium in which plants are growing or are to be planted, or they can be sprayed on, dusted on or applied as a cream or paste formulation, or they can be applied as a vapour or as slow release granules. Application can be to any part of the plant including the foliage, stems, branches or roots, or to soil surrounding the roots, or to the seed before it is planted; or to the soil generally, to paddy water or to hydroponic culture systems. The invention compounds may also be injected into plants or sprayed onto vegetation using electrodynamic spraying techniques or other low volume methods.

The term "plant" as used herein includes seedlings, bushes and trees. Furthermore, the fungicidal method of the invention includes preventative, protectant, prophylactic and eradicator treatment.

The compounds are preferably used for agricultural and horticultural purposes in the form of a composition. The type of composition used in any instance will depend upon the particular purpose envisaged.

The compositions may be in the form of dustable powders or granules comprising the active ingredient (invention compound) and a solid diluent or carrier, for example fillers such as kaolin, bentonite, kieselguhr, dolomite, calcium carbonate, talc, powdered magnesia, Fuller's earth, gypsum, diatomaceous earth and China

clay. Such granules can be preformed granules suitable for application to the soil without further treatment. These granules can be made either by impregnating pellets of filler with the active ingredient or by pelleting a mixture of the active ingredient and powdered filler. Compositions for dressing seed may include an agent (for example a mineral oil) for assisting the adhesion of the composition to the seed; alternatively the active ingredient can be formulated for seed dressing purposes using an organic solvent (for example N-methylpyrrolidone, propylene glycol or dimethylformamide). The compositions may also be in the form of wettable powders or water dispersible granules comprising wetting or dispersing agents to facilitate the dispersion in liquids. The powders and granules may also contain fillers and suspending agents.

Emulsifiable concentrates or emulsions may be prepared by dissolving the active ingredient in an organic solvent optionally containing a wetting or emulsifying agent and then adding the mixture to water which may also contain a wetting or emulsifying agent. Suitable organic solvents are aromatic solvents such as alkylbenzenes and alkylnaphthalenes, ketones such as isophorone, cyclohexanone, and methylcyclohexanone, chlorinated hydrocarbons such as chlorobenzene and trichlorethane, and alcohols such as benzyl alcohol, furfuryl alcohol, butanol and glycol ethers.

Suspension concentrates of largely insoluble solids may be prepared by ball or bead milling with a dispersing agent and including a suspending agent to stop the solid settling.

Compositions to be used as sprays may be in the form of aerosols wherein the formulation is held in a container under pressure in the presence of a propellant, eg. fluorotrichloromethane or dichlorodifluoromethane.

The invention compound may be mixed in the dry state with a pyrotechnic mixture to form a composition suitable for generating in enclosed spaces a smoke containing the compounds.

Alternatively, the compounds may be used in a microencapsulated form. They may also be formulated in biodegradable polymeric formulations to obtain a slow, controlled release of the active substance.

By including suitable additives, for example additives for improving the distribution, adhesive power and resistance to rain on treated surfaces, the different compositions can be better adapted for various utilities.

The invention compounds can be used as mixtures with fertilisers (eg. nitrogen-, potassium- or phosphorus-containing fertilisers). Compositions comprising only granules of fertiliser incorporating, for example coated with, the compound are preferred. Such granules suitably contain up to 25% by weight of the compound. The invention therefore also provides a fertiliser composition comprising a fertiliser and the compound of general formula (I) or a salt or metal complex thereof.

Wettable powders, emulsifiable concentrates and suspension concentrates will normally contain surfactants eg. a wetting agent, dispersing agent, emulsifying agent or suspending agent. These agents can be cationic, anionic or non-ionic agents.

Suitable cationic agents are quaternary ammonium compounds, for example cetyltrimethylammonium bromide. Suitable anionic agents are soaps, salts of aliphatic monoesters of sulphuric acid (for example sodium lauryl sulphate), and salts of sulphonated aromatic compounds (for example sodium dodecylbenzenesulphonate, so-

dium, calcium or ammonium lignosulphonate, butyl-naphthalene sulphonate, and a mixture of sodium diisopropyl- and triisopropyl-naphthalene sulphonates).

Suitable non-ionic agents are the condensation products of ethylene oxide with fatty alcohols such as oleyl or cetyl alcohol, or with alkyl phenols such as octyl- or nonyl-phenol and octylcresol. Other non-ionic agents are the partial esters derived from long chain fatty acids and hexitol anhydrides, the condensation products of the said partial esters with ethylene oxide, and the lecithins. Suitable suspending agents are hydrophilic colloids (for example polyvinylpyrrolidone and sodium carboxymethylcellulose), and swelling clays such as bentonite or attapulgit.

Compositions for use as aqueous dispersions or emulsions are generally supplied in the form of a concentrate containing a high proportion of the active ingredient, the concentrate being diluted with water before use. These concentrates should preferably be able to withstand storage for prolonged periods and after such storage be capable of dilution with water in order to form aqueous preparations which remain homogeneous for a sufficient time to enable them to be applied by conventional spray equipment. The concentrates may conveniently contain up to 95%, suitably 10-85%, for example 25-60%, by weight of the active ingredient. After dilution to form aqueous preparations, such preparations may contain varying amounts of the active ingredient depending upon the intended purpose, but an aqueous preparation containing 0.0005% or 0.01% to 10% by weight of active ingredient may be used.

The compositions of this invention may contain other compounds having biological activity, eg. compounds having similar or complementary fungicidal activity or which plant possess plant growth regulating, herbicidal or insecticidal activity.

A fungicidal compound which may be present in the composition of the invention may be one which is capable of combating ear diseases of cereals (eg. wheat) such as Septoria, Gibberella and Helminthosporium spp., seed and soil-borne diseases and downy and powdery mildews on grapes and powdery mildew and scab on apple etc. By including another fungicide, the composition can have a broader spectrum of activity than the compound of general formula (I) alone. Further the other fungicide can have a synergistic effect on the fungicidal activity of the compound of general formula (I). Examples of fungicidal compounds which may be included in the composition of the invention are carbendazim, benomyl, thiophanate-methyl, thiabendazole, fuberidazole, etridazole, dichlofluanid, cymoxanil, oxadixyl, ofurace, metalazyl, furalaxyl, benalaxyl, fosetyl-aluminum, fenarimol, iprodione, prothiocarb, procymidone, vinclozolin, penconazole, myclobutanil, propamocarb, R0151297, diniconazole, pyazophos, ethirimol, ditalimfos, tridemorph, triforine, nuarimol, triazbutyl, guazatine, triacetate salt of 1,1'-iminodi-(octamethylene)diguandine, buthiobate, propiconazole, prochloraz, flutriafol, hexaconazole, (2RS, 3RS)-2-(4-chlorophenyl)-3-cyclopropyl-1-(1H-1,2,4-triazol-1-yl)butan-2-ol, (RS)-1-(4-chlorophenyl)-4,4-dimethyl-3-(1H-1,2,4-triazol-1-ylmethyl)pentan-3-ol, DPX H6573(1-(bis-4-fluorophenyl)methylsilyl)methyl)-1H-1,2,4-triazole, triadimefon, triademenol, diclobutrazol, fenpropimorph, pyrifenoxy, fenpropidin, chlorozolinate, imazalil, fenfuram, carboxin, oxycarboxin, methfuroxam, dodemorph, BAS 454, blastidicin S, kasugamycin, edifenphos, Kitazin P, cycloheximide, phthalide,

probenazole, isoprothiolane, tricyclazole, 4-chloro-N-(cyano(ethoxy)methyl)benzamide, pyroquilon, chlorbenzthiazole, neosozin, polyoxin D, validamycin A, mepronil, flutolanil, pencyuron, diclomezine, phenazin oxide, nickel dimethyldithiocarbamate, techlofthalam, bitertanol, bupirimate, etaconazole, hydroxyisoxazole, streptomycin, cyprofuram, biloxazol, quinomethionate, dimethirimol, 1-(2-cyano-2-methoxyiminoacetyl)-3-ethyl urea, fenapanil, tolclofosmethyl, pyroxyfur, polyram, maneb, mancozeb, captafol, chlorothalonil, anilazine thiram, captan, folpet, zineb, propineb, sulphur, dinocap, dichlone, chloroneb, binapacryl, nitrothalisopropyl, dodine, dithianon, fentin hydroxide, fentin acetate, tecnazene, quintozone, dicloran, copper containing compounds such as copper oxychloride, copper sulphate and Bordeaux mixture, and organomercury compounds.

The compounds of general formula (I) can be mixed with soil, peat or other rooting media for the protection of plants against seed-borne, soil-borne or foliar fungal diseases.

Suitable insecticides which may be incorporated in the composition of the invention include pirimicarb, dimethoate, demeton-s-methyl, formothion, carbaryl, isoprocarb, XMC, BPMC, carbofuran, carbosulfan, diazinon, fenthion, fenitrothion, phenthoate, chlorpyrifos, isoxathion, propaphos, monocrotophas, buprofesin, ethroproxyfen and cycloprothrin.

Plant growth regulating compounds are compounds which control weeds or seedhead formation, or selectively control the growth of less desirable plants (eg. grasses).

Examples of suitable plant growth regulating compounds for use with the invention compounds are the gibberellins (eg. GA₃, GA₄ or GA₇), the auxins (eg. indoleacetic acid, indolebutyric acid, naphthoxyacetic acid or naphthylacetic acid), the cytokinins (eg. kinetin, diphenylurea, benzimidazole, benzyladenine or benzylaminopurine), phenoxyacetic acids (eg. 2,4-D or MCPA), substituted benzoic acid (eg. triiodobenzoic acid), morphactins (eg. chlorfluoroecol), maleic hydrazide, glyphosate, glyphosine, long chain fatty alcohols and acids, dikegulac, paclobutrazol, fluoridamid, mefluidide, substituted quaternary ammonium and phosphonium compounds (eg. chloromequat chlorphonium or mepiquatchloride), ethephon, carbetamide, methyl-3,6-dichloroanisate, daminozide, asulan, abscisic acid, isopyrimol,

The following Examples illustrate the invention. Throughout these Examples, the term 'ether' refers to diethyl ether; chromatography was carried out using silica gel as the solid phase; magnesium sulphate was used to dry solutions; and reactions involving water- or air-sensitive intermediates were performed under atmospheres of nitrogen. Temperatures are expressed in degrees centigrade.

Where shown, infrared and nmr data are selective; no attempt is made to list every absorption. The following abbreviations are used throughout:

DMF = N,N-dimethylformamide
g = gramme(s)
mmol = millimole(s)
ml = milliliter(s)
mmHg = millimetres pressure of mercury
M.P. = melting point

delta = chemical shift
CDCl₃ = deuteriochloroform
s = singlet
d = doublet
t = triplet
br = broad

-continued

nmr = nuclear magnetic resonance

EXAMPLE 1

This Example illustrates the preparation of E-methyl 2-[2'-(6''-chloropyrazin-2''-yloxy)phenyl]-3-methoxypropenoate (Compound No. 2 of Table I).

2-Hydroxyphenylacetic acid (50 g) was added to a solution of hydrogen chloride in methanol [prepared from acetyl chloride (25 ml) and methanol (250 ml)]. The solution was stirred at room temperature for three hours and then allowed to stand overnight (fifteen hours). The resulting mixture was concentrated under reduced pressure, and the residue was taken up in ether (250 ml) and washed with an aqueous solution of sodium bicarbonate until effervescence ceased. The ethereal solution was dried and then concentrated under reduced pressure and the resulting solid was recrystallized from ether/petrol to afford methyl 2-hydroxyphenylacetate (50 g; 92% YIELD) as white, powdery crystals, M.P. 70°-72° C.; infrared maxima (nujol mull): 3420, 1715 cm⁻¹; ¹H nmr (CDCl₃, 90 MHz): delta 3.70 (2H, s), 3.75 (3H, s), 6.80-6.95 (2H, m), 7.05-7.10 (1H, m), 7.15-7.25 (1H, m), 7.40 (1H, s) ppm.

Methyl 2-hydroxyphenylacetate (21.0 g) was dissolved in dry DMF (200 ml), and dry potassium carbonate (19.35 g) was added in one portion. Benzyl bromide (23.94 g) in dry DMF (50 ml) was added dropwise to this mixture, with stirring, at room temperature. After eighteen hours the mixture was poured into water (500 ml) and extracted with ether (2×400 ml). The extracts were washed with water (3×150 ml) and brine (100 ml), dried and filtered through silica gel (50 g; Merck 60), then concentrated under reduced pressure to afford a yellow oil. Distillation at 160° C. and 0.05 mmHg afforded methyl 2-benzyloxyphenylacetate as a clear, colourless oil (26.99 g; 83% yield), infrared maximum (film): 1730 cm⁻¹; ¹H nmr (CDCl₃, 90 MHz): delta 3.60 (3H, s), 3.75 (2H, s), 4.10 (2H, s), 6.80-7.40 (9H, m) ppm.

Methyl 2-benzyloxyphenylacetate (26.99 g) and methyl formate (126.62 g) in dry DMF (300 ml) were added dropwise to a stirred suspension of sodium hydride (50% disp. in oil, 10.13 g) in DMF (300 ml) at 0° C. After stirring at 0° C. for two hours the mixture was poured into water (1000 ml) and washed with ether (2×150 ml). The aqueous layer was acidified to pH4 with 6M hydrochloric acid then extracted with ether (2×350 ml). The extracts were dried and concentrated under reduced pressure to afford crude methyl 3-hydroxy-2-[2'-benzyloxyphenyl]propenoate as a yellow oil, infrared maxima (film): 1720, 1660 cm⁻¹.

The crude methyl 3-hydroxy-2-(2'-benzyloxyphenyl)propenoate was dissolved in dry DMF (100 ml) and potassium carbonate (29.0 g) was added in one portion. Dimethyl sulphate (16.00 g) in dry DMF (10 ml) was then added dropwise with stirring. After ninety minutes, water (300 ml) was added and the solution was extracted with ether (2×300 ml). After washing with water (3×150 ml) and brine, the extracts were dried and concentrated under reduced pressure, and the resulting yellow oil solidified on trituration with ether/petrol. Recrystallization from dry methanol afforded E-methyl 3-methoxy-2-(2'-benzyloxyphenyl)propenoate as a white, crystalline solid (5.44 g, 17% yield from methyl 2-benzyloxyphenylacetate), M.P. 76°-77° C.; infrared maxima (nujol mull): 1710, 1640 cm⁻¹; ¹H nmr

(CDCl₃, 90 MHz): delta 3.63 (3H, s), 3.75 (3H, s), 5.05 (2H, s), 6.80–7.40 (9H, m), 7.50 (1H, s) ppm.

E-methyl 3-methoxy(2'-benzyloxyphenyl)propenoate (5.44 g) was dissolved in ethyl acetate (50 ml) and 5% palladium on carbon (0.25 g) was added. The stirred mixture was hydrogenated at three atmospheres pressure, with stirring, until no more hydrogen was taken up, then filtered through celite and silica gel (50 g, Merck 60). Concentration of the filtrate under reduced pressure afforded E-methyl 3-methoxy-2-(2'-hydroxyphenyl)propenoate as a white crystalline solid (3.76 g; 99% yield), M.P. 125°–126° C.; infrared maxima (nujol mull): 3400, 1670 cm⁻¹; ¹H nmr (CDCl₃, 270 MHz): delta 3.80 (3H, s), 3.90 (3H, s), 6.20 (1H, s), 6.80–7.00 (2H, m), 7.10–7.30 (2H, m), 7.60 (1H, s) ppm.

E-Methyl 3-methoxy-2-(2'-hydroxyphenyl)propenoate (0.5 g) and 2,6-dichloropyrazine (1.79 g) were dissolved in dry DMF (10 ml) and then sodium hydride (0.24 g, 50% dispersion in oil) was added in portions. After stirring for 30 minutes, water was added dropwise. The reaction mixture was then poured into water (50 ml) and extracted with ether (2 × 100 ml). The ether layers were combined, washed with water (3 × 100 ml) and brine (50 ml) and then dried and filtered. Removal of the solvent under reduced pressure afforded a yellow oil which was purified by chromatography on silica gel (eluent ether) to give the title compound as a viscous yellow oil (75 mg); ¹H nmr (CDCl₃): delta 3.75 (3H, s), 3.80 (3H, s), 7.50 (1H, s), 8.20 (1H, s), 8.30 (1H, s) ppm.

EXAMPLE 2

This Example illustrates the preparation of E-methyl 3-methoxy-2-[2'-(4''-chloro-6''-methoxy-S-triazin-2''-yloxy)propenoate (compound No. 72 of Table 1).

A solution of E-methyl 3-methoxy-2-(2'-hydroxyphenyl)propenoate (0.61 g, prepared as in Example 1) in acetone (20 ml) was stirred with anhydrous potassium carbonate (0.20 g) at room temperature for 45 minutes and then 2,4-dichloro-6-methoxy-S-triazine (0.48 g) was added. After 2 days water (13 ml) was added to the stirred mixture and after a further 1 hour the reaction mixture was diluted with water and extracted with ether (2x). The extracts were dried and concentrated under reduced pressure to give a pale yellow oil which crystallised on standing. Recrystallisation from cyclohexane afforded the title compound as a white crystalline solid (0.33 g), m.pt. 121°–123° C.; ¹H NMR (CDCl₃, 90 MHz); delta 3.61 (3H, s); 3.75 (3H, s); 3.95 (3H, s); 7.1–7.4 (4H, m); 7.45 (1H, s) ppm.

EXAMPLE 3

This Example illustrates the preparation of E-methyl 3-methoxy-2-[2'-(4'',6''-dichloro-S-triazin-2''-yloxy)phenyl]propenoate (Compound No. 29 of Table 1).

A solution of E-methyl 3-methoxy-2-(2'-hydroxyphenyl)propenoate (2.08 g, prepared as in Example 1) in acetone (70 ml) was stirred with potassium carbonate (0.69 g) at 0.20–5° C. 2,4,6-Trichloro-S-triazine (1.85 g) and water (45 ml) were added and the mixture stirred vigorously for 3.5 hours at 0°–5° C. The reaction mixture was then diluted with water and extracted with ether. The extract was washed with dilute aqueous sodium hydroxide (2x) and water and then dried. Removal of the solvent under reduced pressure left a pale yellow solid residue which was purified by black chromatography (silica gel, petroleum ether-ether) to give the title compound as a white crystalline solid (0.16 g), m.pt. 141°–142.5° C.; ¹H NMR (CDCl₃, 90 MHz); delta

3.62 (3H, s); 3.77 (3H, s); 7.1–7.5 (4H, m); 7.46 (1H, s) ppm.

The following are examples of compositions suitable for agricultural and horticultural purposes which can be formulated from the compounds of the invention. Such compositions form another aspect of the invention. Percentages are by weight.

EXAMPLE 4

An emulsifiable concentrate is made up by mixing and stirring the ingredients until all are dissolved.

Compound No. 2 of Table I	10%
Benzyl alcohol	30%
Calcium dodecylbenzenesulphonate	5%
Nonylphenolethoxylate (13 moles ethylene oxide)	10%
Alkyl benzenes	45%

EXAMPLE 5

The active ingredient is dissolved in methylene dichloride and the resultant liquid sprayed on to the granules of attapulgite clay. The solvent is then allowed to evaporate to produce a granular composition.

Compound No. 2 of Table I	5%
Attapulgite granules	95%

EXAMPLE 6

A composition suitable for use as a seed dressing is prepared by grinding and mixing the three ingredients.

Compound No. 2 of Table I	50%
Mineral oil	2%
China clay	48%

EXAMPLE 7

A dustable powder is prepared by grinding and mixing the active ingredient with talc.

Compound No. 2 of Table I	5%
Talc	95%

EXAMPLE 8

A suspension concentrate is prepared by ball milling the ingredients to form an aqueous suspension of the ground mixture with water.

Compound No. 2 of Table I	40%
Sodium lignosulphonate	10%
Bentonite clay	1%
Water	49%

This formulation can be used as a spray by diluting into water or applied directly to seed.

EXAMPLE 9

A wettable powder formulation is made by mixing together and grinding the ingredients until all are thoroughly mixed.

Compound No. 2 of Table I	25%	5
Sodium lauryl sulphate	2%	
Sodium lignosulphonate	5%	
Silica	25%	
China clay	43%	

EXAMPLE 10

Compounds 2, 29 and 72 of Table I were tested against a variety of foliar fungal diseases of plants. The technique employed was as follows.

The plants were grown in John Innes Potting Compost (No. 1 or 2) in 4 cm diameter minipots. The test compounds were formulated either by bead milling with aqueous Dispersol T or as a solution in acetone or acetone/ethanol which was diluted to the required concentration immediately before use. For the foliage diseases, the formulations (100 ppm active ingredient) were sprayed onto the foliage and applied to the roots of the plants in the soil. The sprays were applied to maximum retention and the root drenches to a final concentration equivalent to approximately 40 ppm a.i./dry soil. Tween 20, to give a final concentration of 0.05%, was added when the sprays were applied to cereals.

For most of the tests the compound was applied to the soil (roots) and to the foliage (by spraying) one or two days before the plant was inoculated with the disease. An exception was the test on *Erysiphe graminis* in which the plants were inoculated 24 hours before treatment. Foliar pathogens were applied by spray as spore suspensions onto the leaves of test plants. After inoculation, the plants were put into an appropriate environment to allow infection to proceed and then incubated until the disease was ready for assessment. The period between inoculation and assessment varied from four to fourteen days according to the disease and environment.

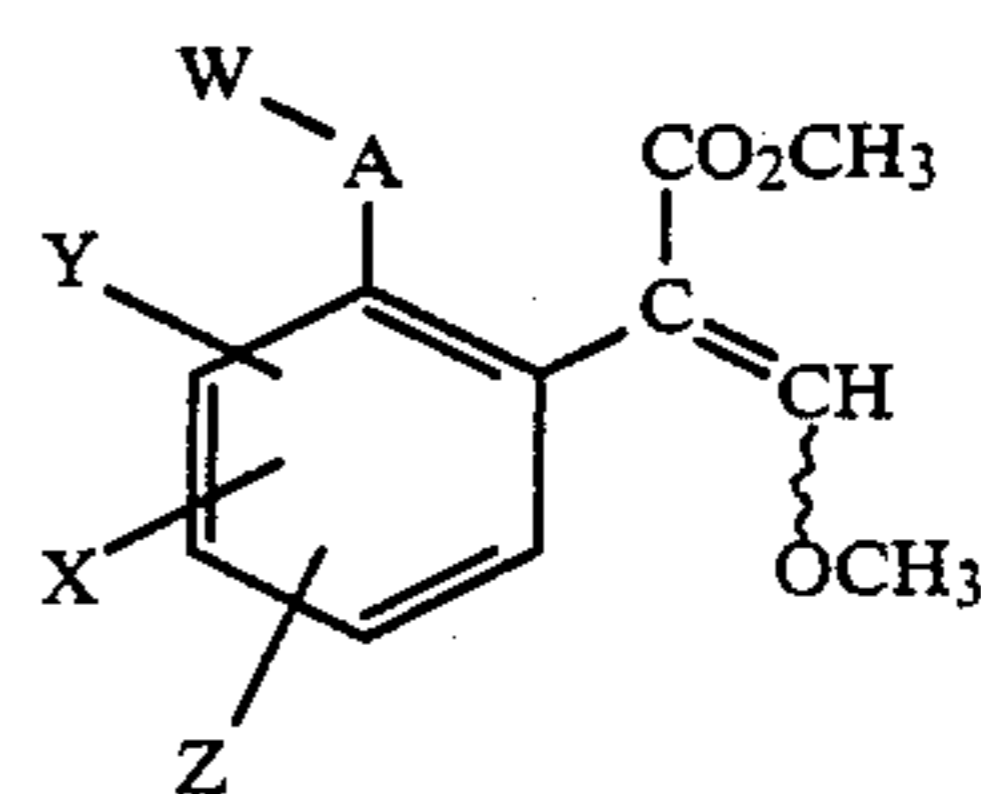
The disease control was recorded by the following grading:

- 4=no disease
 - 3=trace — 5% of disease on untreated plants
 - 2=6-25% of disease on untreated plants
 - 1=26-59% of disease on untreated plants
 - 0=60-100% of disease on untreated plants
- The results are shown in Table II.

TABLE II

COM- POUND NO. (TABLE I)	<i>PUCCINIA</i> <i>RECONDITA</i> (WHEAT)	<i>ERYSIPHE</i> <i>GRAMINIS</i> (BARLEY)	<i>VENTURIA</i> <i>INAEQUALIS</i> (APPLE)	<i>PYRICU-</i> <i>LARIA</i> <i>ORYZAE</i> (RICE)	<i>CERCOSPORA</i> <i>ARACHIDICOLA</i> (PEANUTS)	<i>PLASMOPARA</i> <i>VITICOLA</i> (VINES)	<i>PHYTOPHTHORA</i> <i>INFESTANS</i> (TOMATO)
2	4	4	4	4	4	4	3
29	—	0	—	3	—	4	0
72	0	0	2	0	—	4	3

— Not tested



and stereoisomers thereof, wherein X, Y and Z, which are the same or different, are hydrogen, halogen, hydroxy, C₁₋₆ alkyl, C₂₋₆ alkenyl optionally substituted with phenyl, furyl, thienyl or pyridyl, phenyl, C₂₋₆ alkynyl optionally substituted with phenyl, C₁₋₆ alkoxy, phenoxy, phenyl(C₁₋₆)alkyl, phenyl(C₁₋₆)alkoxy, phenoxy(C₁₋₆)alkyl, C₁₋₆ alkanoyl, benzoyl, amino, C₁₋₆ alkanoylamino, benzoylamino, furoylamino, thienylcarbonylamino, nitro, cyano, —CO₂R¹, —CONR²R³ or —COR⁴, the alkyl moieties of any of the foregoing groups being optionally substituted with hydroxy, halogen, C₁₋₄ alkoxy or

C₁₋₄ alkoxy carbonyl, the phenyl or heterocyclic moieties of any of the foregoing groups being optionally substituted with one or more of halogen, hydroxy, C₁₋₄ alkyl, C₁₋₄ alkoxy, trifluoromethyl, trifluoromethoxy, phenoxy, benzyloxy, nitro, amino, phenyl, carboxy,

C₁₋₆ alkoxy carbonyl, cyano, C₁₋₆ alkylcarbonylamino or methylenedioxy and any of the foregoing amino moieties being optionally substituted with N-phenyl or N—C₁₋₆ alkyl;

W is a C-linked pyrazinyl ring optionally substituted with halogen,

nitro,

C₁₋₄ alkyl which is itself optionally substituted with halogen,

hydroxy or

C₁₋₄ alkoxy,

C₁₋₄ alkoxy which is itself optionally substituted with halogen,

hydroxy or

C₁₋₄ alkoxy,

phenoxy which is itself optionally substituted with halogen,

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hydroxy,
amino which is itself optionally substituted with
C₁₋₄ alkyl, or
cyano,

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or W is benzopyrazin-2-yl; A is oxygen or sulphur;
and R¹, R², R³, and R⁴, which are the same or
different, are hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl,
C₃₋₆ cycloalkyl(C₁₋₆)alkyl, C₂₋₆ alkenyl, C₂₋₆ alkyl-
nyl, phenyl or phenyl(C₁₋₆)alkyl, in which the

We claim:

1. A compound having the formula (I):

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phenyl moieties are optionally substituted as defined above.

2. A compound according to claim 1 wherein X, Y and Z which are the same or different, are hydrogen, fluoro, chloro, bromo, hydroxy, methyl, methoxy trifluoromethyl, methylamino or dimethylamino.

3. A compound according to claim 1 which is in the form of the (E)-isomer.

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4. A compound according to claim 2 in which X, Y, and Z are all hydrogen.

5. A fungicidal composition comprising, as an active ingredient, a fungicidally effective amount of a compound according to claim 1 together with a fungicidally acceptable carrier or diluent therefor.

6. A method of combating fungi which comprises applying to a plant, to seed of a plant, or to a locus of the plant or seed, an effective amount of a compound as claimed in claim 1.

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